

Diabetes Drugs by Class

Alpha-glucosidase Inhibitors

Alpha Glucosidase (AL-fa gloo-KOS-ih-dayss in-HIB-it-ers) slow the absorption of the starches you eat. Names are **PRECOSE or acarbose** and **GLYSET or miglitol**. Treat lows only with glucose. Will not create low sugars when used alone.

D-Phenylalanine

D-Phenylalanine (dee-fen-nel-AL-ah-neen) derivatives help your pancreas make more insulin quickly. Name: **PRANDIN or repaglinide**. Take just before eating. Do not take if skipping a meal. Do not take with Gemfibrozil, and avoid grapefruit juice. Has ability to lower sugars to too low.

Meglitinide

Meglitinide is a type 2 oral medication that helps your pancreas make more insulin right after meals. Name: **STARLIX or nateglinide**. Take just before eating, skip dose if not eating.

Sulfonylureas

Sulfonylureas (SUL-fah-nil-YO-ree-ahs) stimulate your pancreas to make more insulin so have the potential to make glucose go too low. They also contribute to weight gain, especially when used with insulin. Name: **Glucotrol (glipizide), Micronase. Diabeta or Glynase** are all **glyburide**. The one used most often now is **AMARYL or glimepiride**.

Biguanides

Biguanides (by-GWAN-ides) decrease the amount of glucose made by your liver. Name is **METFORMIN or glucophage**. If a liquid, called **RIOMET**. Take with food to decrease nausea when starting it. Follow your B12 levels to sure sufficient. Do not take on days of surgery, illness, or dye studies until eating and drinking normally, and urinating well.

DPP-IV Inhibitors

DPP-IV inhibitors boost production of the incretin gut hormones GLP-1 and GIP to help lower blood glucose levels. It increases insulin production and cuts down on glucagon production to lessen glucose from the liver. Do not make sugars go too low, if used alone. Names: **JANUVIA sitagliptin, ONGLYZA saxagliptin, TRADJENTA linagliptin, NESINA alogliptin**, (Merck has one coming – omargliptin). **Report any new joint pain immediately.**

Thiazolidinedione

Thiazolidinedione (THIGH-ah-ZO-li-deen-DYE-owns) make you more sensitive to insulin. Name: **AVANDIA or rosiglitazone**, which is not available except through specialty pharmacy. **ACTOS or pioglitazone** is available. Some weight gain, not used in Congestive Heart Failure, but has long effect on glucose control. Best used in low dosage. Bone loss in females and bladder cancer in men have been reported.

SGLT-2s

This class of oral medications works by slowing down the glucose-recovery process initiated by the kidneys. **INVOKANA or canagliflozin**. Side effect is weight loss and blood pressure improvement. Some urinary tract infections and yeast, easily treated with over the counter medication. Uncircumcised men not good candidates for this. May pose low blood pressure if glucosuria (sugar in the urine) is extreme. Doctor may lower blood pressure medications to start with and ask you to drink several extra glasses of water per day at the start. **FARXGIA or dapagliflozin** is the second drug in this class with many more on the way. Also **JARDIANCE or empagliflozin** is available. **STEGLATRO or ertugliflozin** also coming in combination pills. **Don't take if you can't drink water.**

GLP-1 Agonists

GLP-1 agonists, administered via injectable devices, work in conjunction with other drugs to help people with type 2 maintain control. Names: **BYETTA (exenatide)** taken twice a day, **VICTOZA (liraglutide)** taken once per day, and **BYDUREON (extended release exenatide)** taken weekly, from a BCise pen.

Works to decrease appetite, hold liver from releasing too much glucose, increase the insulin production, slow stomach emptying and lead to weight loss in ¾ of the persons who use these products.

TANZEUM (albiglutide) weekly injection FDA approved 4/15/2014 out of business in 2017.

09/19/2014 **TRULICITY (dulaglutide)** once weekly
8/01/16 **ADLYXIN or (lixisenatide)** once daily prefilled pen, when combined with glargine, with an uncontrolled A1c, start at 15 units (15 u glargine and 5mcg of lixisenatide). If patient inadequately controlled on 30-60 units of basal insulin dose is 30 units daily (30 units glargine and 10mcg lixisenatide). Max dose is 60. Green pen

10-19-17 FDA approved **OZEMPIC (semaglutide)** a weekly glp-1RA from Novo as an injection, being studied to be an oral. Comes in .25 for a starting dose once weekly, working up to the .5mg per week then on to 1.0 dose in a prefilled pen.

AMYLIN

SYMLIN, pramlintide is an injectable medication used along with mealtime insulin doses to control blood sugar levels in adults. Amylin was co-secreted with insulin. The synthetic version, Symlin, replaces the effects of amylin. So slower gastric emptying, less sugar from the liver released and satiety after eating. Much like the GLP effect, but does not increase insulin production- it was made with the insulin before diabetes occurred.

BROMOCRIPTINE

CYCLOSET is a medication that works on the hypothalamus, an area in the brain to decrease your insulin resistance. Used at low levels, it compliments the use of the GLP-1 drugs.

Combination Oral Medicines

Metformin and pioglitazone have lost patent:

Metaglip (metformin + glipizide)	Kazano (alogliptin + metformin)
Synjardy (empagliflozin+metformin)	Oseni (alogliptin + pioglitazone)
ActoPlus (Actos + metformin)	Invokamet (Invokana +metformin)
Janumet (Januvia + metformin)	Januvisync (Januvia + simvastatin)
Jenaduetto (Tadjenta + metformin)	Glyxambi (Tadjenta + Jardiance)
Kombiglyze (Onglyza + metformin)	Steglujan (ertugliflozin + Januvia)
Stegluromet (ertugliflozin + metformin)	Xigduo (Farxiga + metformin)
Qtern (dapagliflozin + saxagliptin (Farxiga and Onglyza)	

Miscellaneous Agents

These agents have a smaller effect on lowering blood sugar. They may be used in cases when just a little help is needed or where other choices are limited.

WELCHOL colessevelam is a medication used to bring LDL cholesterol down, but also has a mild effect on glucose to help along with other medications to lower A1c.

RANEXA ranolazine approved for use in angina but has glucose lowering properties. Action results from increased efficiency of myocardial oxygen use when myocardial metabolism is shifted away from fatty acid oxidation toward glucose oxidation. Don't crush tablets and avoid grapefruit juice.

From SANOFI

TOUJEO This is **insulin** glargine (or Lantus u100) that is more concentrated in a U-300 concentration. The fact that less insulin is needed per depot of injection, the profile is much smoother baseline coverage that lasts better for a 24 hour period than Lantus did. Dose adjustment made on the pen dial, so just dial dose like usual.

Adlxyin, or lixisenatide. Is a **GLP-1** alone. Adlxyin comes in pre-filled pen.

Green pen is the low multiple dose pen. Starting dose is 10mcg daily for 14 days.

Burgundy pen is the multiple dose pen and is 20 mcg daily starting on day 15 of treatment.

SOLIQUA 100/33 a prefilled pen with a fixed dose of insulin glargine 100U/ml and lixisenatide 33 micrograms/ml and is indicated for once daily dosing covering 15 to 60 units of insulin glargine and 5 to 20 micrograms of lixisenatide. Take within an hour of the first meal of the day. Available Jan 2017 in U.S. Comes with 300 units per pen and 5 pens per box. Start dosing at 15 units. Refrigerate new pens, once opened is good for 14 days and should be stored at room temp. Dosing goes from 15-60 units.

ADMELOG a bio-similar lispro or mealtime insulin (like Humalog) from **Sanofi**

FDA approved 12-11-17

From NOVO NORDISK

9-25-2015 **TRESIBA u-100 AND u-200** insulin degludec

From Novo Nordisk, a long acting, human basal insulin, given once daily. May be at the same time, or any time, of day. Not to be repeated within an 8 hour period. Either pen does the calculations in the dial so what the patient dials is the actual number of units they are getting. Store pens in refrigerator, without freezing. An open pen in use is good for 56 days, if temp not too hot or freezing. Start at 10 units with Type 2's, make adjustments only after 3-4 days of treatment to see steady state. Onset is in one hour, maximum glucose lowering effect seen in 12 hours. Pen displays in 2 unit increments.

*After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

It forms multi-hexamers when injected into sub-q tissue, resulting in a depot. Tresiba is predominantly due to delayed absorption of insulin degludec from the sub-q tissue to the systemic circulation and to a lesser extent due to binding of insulin degludec to circulating albumin. Not studied in children under 18 and is pregnancy Class C.

XULTOPHY 100/3.6 Released Dec 2017. From Novo: Liraglutide with Tresiba for a once daily injection that lasts 24 hours. Same time of day dosing for the ease of use would be good. The product is degludec 100u/ml with liraglutide 3.6 mg/ml. The dosing is in single units from 10 -50. Proper dosing is in stomach, arms, upper thighs and legs. To be held in place, plunger pushed down for a count of 6. The pen does need to be primed using the prime marking (first mark) on the pen dose guide. Product should be clear and colorless. Is indicated for persons not controlled on <50 units of basal insulin/ on less than, or equal, to liraglutide of 1.8mg daily. Each unit is 1 unit Tresiba, with 0.036 mg of Victoza. The regular GLP-1 indications and warnings/teachings/ precautions of hypoglycemia apply for this product.

FIASP - insulin aspart, a very rapid acting insulin, from Novo Nordisk, FDA approval given 9-9-2017 Type 1 and Type 2. Fiasp gets speedier absorption out of Niacinamide or B3. Dosing is before a meal or within 20 min of the meal. More physiologic and comes in prefilled pen or vial. Once open vial/ pen only good for 28 days. Use unit for unit for any other bolus insulin. Pen goes up to 80 units per single dose. Vial is 10 ml. Has a more physiologic response, like Afrezza does

From LILLY

HUMALOG U200 insulin lispro From Eli Lilly, Is a concentrated form of Humalog with twice as much per syringe, designed for the person using larger numbers of units per meal. The pen does the conversion so no change in dosing, just that the amount of fluid per injection is half of the usual. Makes a pen last longer.

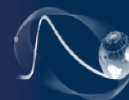
BASAGLAR The first bio-similar insulin to come to the US market. While used by 30% in Europe, just hitting the US market Dec of 2016. It is the glargine molecule grown by Lilly. Expectation is that it will work like the glargine (Lantus) did before. The major difference will be the much lower price of \$316.85 for 5 pens. Appreciably lower than Lantus, Levemir, Toujeo or Tresiba. Has a \$5 copay card for the non-Medicare persons

FROM MANNKIND

AFREZZA An inhaled **insulin** that uses a disposable device with 4, 8, or 12 unit blister packs. Has onset in 10 min and peaks at 180 minutes. Much cleaner look at the baseline with this crisp action. Not for Patients who smoke or have chronic lung disease or former lung cancer. Spirometry needs to be done before initiation, at 6 months of use, and annually thereafter. Not for children. Onset 2.5 min, gone in 2 hrs.

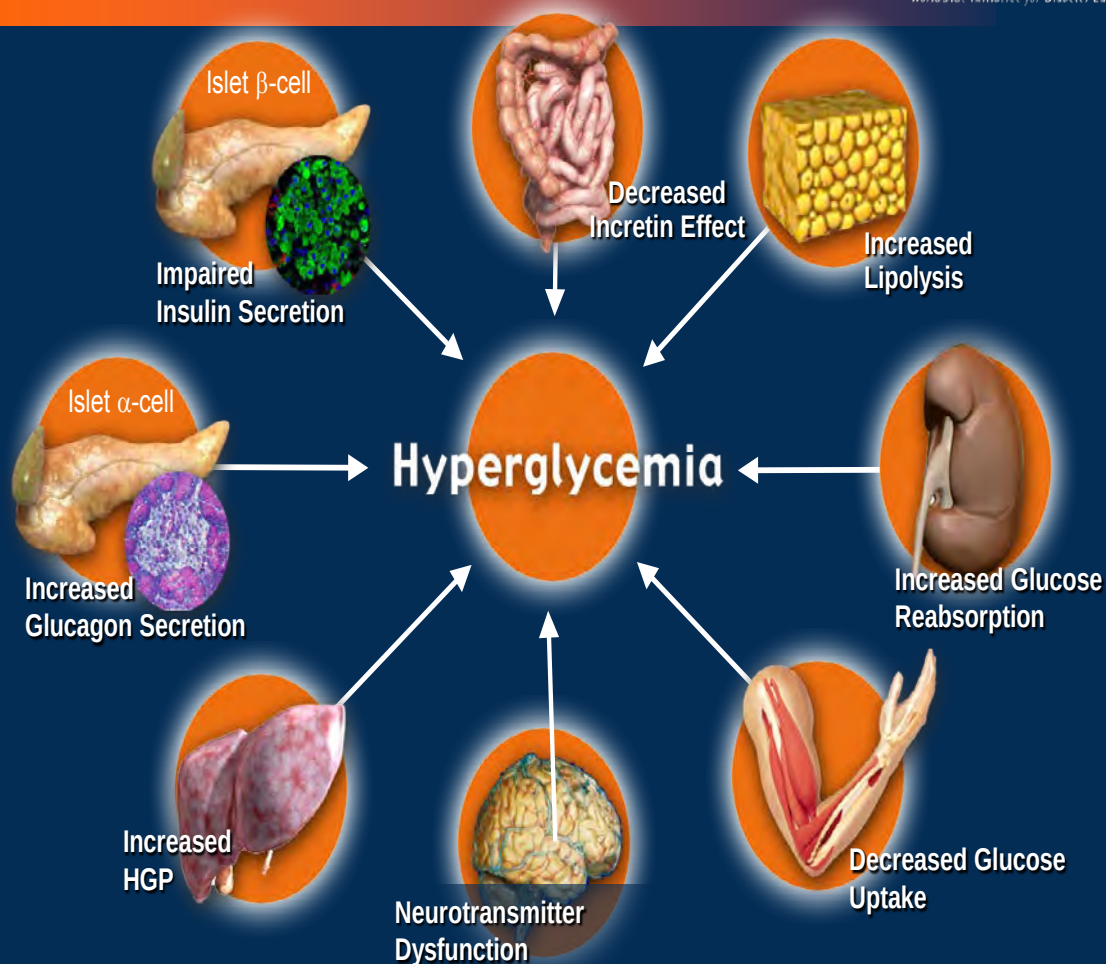
The Jardiance SGLT2i drug and Victoza, a GLP-1 drug have been shown to offer cardiovascular support with lower heart events seen. Invokana did the Canvas trial and showed they were cardiovascularly safe too. Look for the final of the trial with Farxgia this 2018 on kidney and cardiovascular protection and decrease in congestive heart failure. This whole class of medications may all have the same effect.

The Ominous Octet



WorldWIDE

Worldwide Initiative for Diabetes Education



Article Link: <http://diabetes.webmd.com/alpha-glucosidase-inhibitors-for-type-2-diabetes>

Diabetes Health Center

Alpha-Glucosidase Inhibitors for Type 2 Diabetes

Examples

Generic Name	Brand Name
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acarbose	Precose
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miglitol	Glyset
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How It Works

Acarbose and miglitol help keep blood sugar levels within a [target range](#) by slowing the digestion of [complex carbohydrates](#), also called starches. Complex carbohydrates include foods like bread, cereal, grain, pasta, rice, flour, beans, and vegetables like potatoes and corn. These medicines do not change the effect that simple sugars have on [blood](#) sugar. Simple sugars include foods like fruit, juice, milk, honey, desserts, and candy.

The medicine is taken with the first bite of food. These medicines do not cause the [pancreas](#) to produce more [insulin](#). They will not cause [low blood sugar \(hypoglycemia\)](#) unless they are used with other oral medicines for [diabetes](#) or with [insulin](#).

Why It Is Used

Alpha-glucosidase inhibitors help people with [type 2 diabetes](#) whose blood sugar is highest after eating complex carbohydrates.

The medicine may be used alone, with another medicine for diabetes, or with insulin.

How Well It Works

Type 2 diabetes is a disease that can get worse over time, so medicines may need to change. Diabetes medicines work best for people who are being active and eating healthy foods.

When taken with the first bite of food, these medicines have been found to lower blood sugar levels in people who have high blood sugar after eating (postprandial hyperglycemia). Studies have suggested that alpha-glucosidase inhibitors lower [hemoglobin A1c](#) by 0.5% to 0.8%.¹

Side Effects

All medicines have side effects. But many people don't feel the side effects, or they are able to deal with them. Ask your pharmacist about the side effects of each medicine you take. Side effects are also listed in the information that comes with your medicine.

Here are some important things to think about:

- Usually the benefits of the medicine are more important than any minor side effects.
- Side effects may go away after you take the medicine for a while.

- If side effects still bother you and you wonder if you should keep taking the medicine, **call your doctor**. He or she may be able to lower your dose or change your medicine. Do not suddenly quit taking your medicine unless your doctor tells you to.

Call 911 or other emergency services right away if you have:

- Trouble breathing.
- Hives.
- Swelling of your face, lips, tongue, or throat.

Call your doctor if you have:

- Yellow eyes.
- Yellow skin.

Common side effects of this medicine include:

- Passing of gas.
- Feeling bloated.
- Belly pain.
- Diarrhea.

See Drug Reference for a full list of side effects. (Drug Reference is not available in all systems.)

What To Think About

These medicines do not cause low blood sugar or weight gain, but you might have low blood sugar if you don't eat or if you exercise, drink alcohol, or use another medicine that causes low blood sugar. When taking this medicine, low blood sugar can be treated with quick-sugar foods **except** table sugar or regular soda pop, which will not work.

If you pass a lot of gas while taking this medicine, your doctor may suggest a lower dose and then increase the dose slowly. Eating a lower-carbohydrate diet can also help. If you have problems with your digestive system, you might not be able to take this medicine.

1. American Diabetes Association (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. Diabetes Care, 32: 193-203.

METFORMIN or Glucophage

French Lilac, Goat's Rue or Italian Fitch or *Galega officinalis*

So, Metformin came from a plant, and has been used as a tea over 3000 years ago to relieve polyuria (frequent urination) and halitosis (sweet odor on the breath). Both of these are diabetes symptoms. It has been used in the US since 1995 and is the most widely prescribed drug filled yearly worldwide.

The mechanism of Glucophage is not fully understood but believed to decrease the production of glucagon (the hormone that causes sugar to appear in the blood stream) which then decreases the amount of sugar the liver releases. It also helps a bit with the insulin sensitization, getting the glucose or sugar into the cells where it is needed. When used in the Diabetes Prevention Trial, the metformin taking arm of the trial decreased getting diabetes by 31%! It can be started in Pre-Diabetes. The earlier it is taken in the course of diabetes, the longer it is able to control the blood sugars.

Metformin has been suggested to be a cancer preventer-lung, colorectal, endometrial, ovarian, pancreatic, breast, prostate tissues.

Metformin has modest impact on LDL, HDL, triglycerides and is weight neutral. It does not creat hypoglycemia (low blood sugar) by itself.

Several cautions: Take the first doses with food to decrease any nausea that might happen. Nausea, or diarrhea, are expected to go way down, disappear, over time. Some never get symptoms. Metformin is started low, at 500 mg, then increased as you tolerate it (no nausea, no diarrhea). The dose you want to be at is 1000mg in the AM and 1000mg in the PM. After you have been on it awhile, taking with food is not important any longer. This is the most effective range for Metformin. Some do better with Glucophage ER or XR.

If having tests with dye done, surgery, or acutely ill, do not take Metformin that day and up to two days later when once eating and urinating normally. Staff in surgery or x-ray will help you remember this. If taken while the kidneys are trying to clear the dye, it is a big load and the metformin can become concentrated. A problem called Lactic Acidosis can develop- tummy discomfort, trouble breathing. This disappears as the metformin is cleared. People with low function of the kidneys are not candidates for Metformin.

Have B12 checked regularly. We need vitamin B12 to keep our nerves working right. Metformin can interfere with this, so replacement may need to be done. If not, neuropathy (painful nerves) can develop. Once established, taking B12 does not help, so prevention is important. Your providers know this too.

A novel probiotic containing a prebiotic and an antioxidant augments the glucose control and gastrointestinal tolerability of metformin: a case report.

[Greenway F](#), [Wang S](#), [Heiman M](#).

Source

Pennington Biomedical Research Center, Outpatient Clinic, Louisiana State University System, 6400 Perkins Road, Baton Rouge, LA 70808, USA.

Abstract

The gut microbiome plays an important role in regulation of metabolic processes, including digestion, absorption, and synthesis of bioactive molecules that signal physiological host mechanisms. Changes in the human gut microbiome are associated with type 2 diabetes and insulin resistance. Water-soluble dietary fibres like inulin and beta-glucan are fermented in the colon, and beta-glucan increases viscosity. Blueberries improve insulin sensitivity through an antioxidant effect. A probiotic, consisting of purified inulin, sugar-free blueberry pomace extract, and an oat preparation of purified beta-glucan was developed for twice a day (bid) consumption as a smoothie drink to repair the gastrointestinal dysbiosis in type 2 diabetes. A 30-year-old man presented with new onset type 2 diabetes and a fasting glucose (FBS) of 375 mg/dl. Metformin 500 mg bid was initiated and increased to 1 g bid after 1 week. During the first 9 days of metformin treatment, he developed diarrhoea, but his FBS only dropped to 325 mg/dl. The probiotic bid was added on the 9th day of metformin treatment, and after 2 days, his FBS dropped to 175 mg/dl. After 8 weeks on metformin and the probiotic, his blood sugar was 100 mg/dl and he lost 5.5 kg. His stools became soft and formed on the probiotic, reverted to diarrhoea when off of it for 2 days, and returned to normal on resuming the probiotic formulation. Metformin is a safe, effective and inexpensive generic medication favouring weight loss, recommended as initial treatment of type 2 diabetes by the American Diabetes Association. However, a 20% incidence of diarrhoea limits its tolerability. A safe food supplement that can increase the efficacy of metformin and its tolerability, as occurred in this case report, would have significant positive public health consequences. A controlled clinical trial of the probiotic with metformin is planned.

Medication Guide
JANUVIA® (jah-NEW-vee-ah)
(sitagliptin)

Tablets

Read this Medication Guide carefully before you start taking JANUVIA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JANUVIA, ask your doctor or pharmacist.

What is the most important information I should know about JANUVIA?

Serious side effects can happen in people taking JANUVIA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking JANUVIA:

Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels
- kidney problems

Stop taking JANUVIA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JANUVIA?

- JANUVIA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUVIA is not for people with type 1 diabetes.
- JANUVIA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take JANUVIA.
- It is not known if JANUVIA is safe and effective when used in children under 18 years of age.

Who should not take JANUVIA?

Do not take JANUVIA if:

- you are allergic to any of the ingredients in JANUVIA. See the end of this Medication Guide for a complete list of ingredients in JANUVIA.

Symptoms of a serious allergic reaction to JANUVIA may include:

- rash
- raised red patches on your skin (hives)
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

What should I tell my doctor before taking JANUVIA?

Before you take JANUVIA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUVIA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.

Pregnancy Registry: If you take JANUVIA at any time during your pregnancy, talk with your doctor about how you can join the JANUVIA pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.

- are breast-feeding or plan to breast-feed. It is not known if JANUVIA will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUVIA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take JANUVIA?

- Take JANUVIA 1 time each day exactly as your doctor tells you.
- You can take JANUVIA with or without food.
- Your doctor may do blood tests from time to time to see how well your kidneys are working. Your doctor may change your dose of JANUVIA based on the results of your blood tests.
- Your doctor may tell you to take JANUVIA along with other diabetes medicines. Low blood sugar can happen more often when JANUVIA is taken with certain other diabetes medicines. See **“What are the possible side effects of JANUVIA?”**.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JANUVIA at the same time.
- If you take too much JANUVIA, call your doctor or local Poison Control Center right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JANUVIA.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of JANUVIA?

Serious side effects have happened in people taking JANUVIA.

- See **“What is the most important information I should know about JANUVIA?”**.
- **Low blood sugar (hypoglycemia).** If you take JANUVIA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUVIA. Signs and symptoms of low blood sugar may include:

- headache
- drowsiness
- weakness
- dizziness
- confusion
- irritability
- hunger
- fast heart beat
- sweating
- feeling jittery

- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUVIA and call your doctor right away. See “**Who should not take JANUVIA?**”. Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **Kidney problems**, sometimes requiring dialysis

The most common side effects of JANUVIA include:

- upper respiratory infection
- stuffy or runny nose and sore throat
- headache

JANUVIA may have other side effects, including:

- stomach upset and diarrhea
- swelling of the hands or legs, when JANUVIA is used with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.

These are not all the possible side effects of JANUVIA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JANUVIA?

Store JANUVIA at 68°F to 77°F (20°C to 25°C).

Keep JANUVIA and all medicines out of the reach of children.

General information about the use of JANUVIA

Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JANUVIA for a condition for which it was not prescribed. Do not give JANUVIA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JANUVIA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUVIA that is written for health professionals. For more information, go to www.JANUVIA.com or call 1-800-622-4477.

What are the ingredients in JANUVIA?

Active ingredient: sitagliptin

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. The tablet film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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USMG-T-04311305R011

MEDICATION GUIDE Rx ONLY
ONGLYZA (on-GLY-zah)
(saxagliptin)
tablets

Read this Medication Guide carefully before you start taking ONGLYZA (saxagliptin) and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have any questions about ONGLYZA, ask your healthcare provider.

What is the most important information I should know about ONGLYZA?

Serious side effects can happen to people taking ONGLYZA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking ONGLYZA:

Tell your healthcare provider if you have ever had

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with ONGLYZA.

Stop taking ONGLYZA and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is ONGLYZA?

- ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.

ONGLYZA® (saxagliptin)

- ONGLYZA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low. However, hypoglycemia may still occur with ONGLYZA. Your risk for getting hypoglycemia is higher if you take ONGLYZA with some other diabetes medicines, such as a sulfonylurea or insulin.
- ONGLYZA is not for people with type 1 diabetes.
- ONGLYZA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take ONGLYZA.

It is not known if ONGLYZA is safe and effective in children younger than 18 years old.

Who should not take ONGLYZA?

Do not take ONGLYZA if you:

- are allergic to any ingredients in ONGLYZA. See the end of this Medication Guide for a complete list of ingredients in ONGLYZA. Symptoms of a serious allergic reaction to ONGLYZA may include:
 - swelling of your face, lips, throat, and other areas on your skin
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

What should I tell my healthcare provider before taking ONGLYZA?

Before you take ONGLYZA, tell your healthcare provider if you:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.

ONGLYZA® (saxagliptin)

- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- Do not split or cut ONGLYZA tablets.
- During periods of stress on the body, such as:
 - fever
 - trauma
 - infection
 - surgery

Contact your healthcare provider right away as your medication needs may change.

- Your healthcare provider should test your blood to measure how well your kidneys are working before and during your treatment with ONGLYZA. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.

ONGLYZA® (saxagliptin)

- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?

ONGLYZA can cause serious side effects, including:

- See **"What is the most important information I should know about ONGLYZA?"**
- **Allergic (hypersensitivity) reactions**, such as:
 - swelling of your face, lips, throat, and other areas on your skin
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

ONGLYZA® (saxagliptin)

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68°F and 77°F (20°C and 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals. For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

ONGLYZA® (saxagliptin)

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ONGLYZA (saxagliptin) tablets

Manufactured by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:

Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850



Bristol-Myers Squibb

1297954A0 / 1256314A4 / 1296566A1

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What are Tradjenta® (linagliptin) tablets?

TRADJENTA is a prescription medicine that is used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

TRADJENTA is not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine).

If you have had inflammation of the pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take TRADJENTA.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about TRADJENTA?

Serious side effects can happen to people taking TRADJENTA, including inflammation of the pancreas (pancreatitis), which may be severe and lead to death. Before you start taking TRADJENTA, tell your doctor if you have ever had pancreatitis, gallstones, a history of alcoholism, or high triglyceride levels.

Stop taking TRADJENTA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

Who should not take TRADJENTA?

Do not take TRADJENTA if you are allergic to linagliptin or any of the ingredients in TRADJENTA.

Symptoms of a serious allergic reaction to TRADJENTA may include rash, itching, flaking or peeling; raised red patches on your skin (hives); swelling of your face, lips, tongue and throat that may cause difficulty breathing or swallowing. If you have any symptoms of a serious allergic reaction, stop taking TRADJENTA and call your doctor right away.

What should I tell my doctor before using TRADJENTA?

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TRADJENTA may affect the way other medicines work, and other medicines may affect how TRADJENTA works.

Especially tell your doctor if you take

- other medicines that can lower your blood sugar, such as a sulfonylurea or insulin.
 - TRADJENTA may cause serious side effects, including low blood sugar (hypoglycemia). If you take TRADJENTA with another medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered while you take TRADJENTA.
 - Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, or feeling jittery.
- rifampin (Rifadin®, Rimactane®, Rifater®, Rifamate®)*, an antibiotic that is used to treat tuberculosis.

Tell your doctor if you are pregnant or planning to become pregnant or are breastfeeding or plan to breastfeed.

What are the possible side effects of TRADJENTA?

The most common side effects of TRADJENTA include stuffy or runny nose, sore throat, cough and diarrhea.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more safety information, please see [Medication Guide and full Prescribing Information](#).

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Replacement Card

If you are already enrolled in the TRADJENTA Savings Card Program and need a replacement card, please call the TRADJENTA Savings Card Program at 1-877-512-4246. Our customer service representatives are available to assist you.

Tradjenta is not cleared through the kidneys, so safe in poor renal function cases.

MEDICATION GUIDE
NESINA (nes-see'-na)
(alogliptin)
tablets

Read this Medication Guide carefully before you start taking NESINA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about NESINA, ask your doctor or pharmacist.

What is the most important information I should know about NESINA?

Serious side effects can happen to people taking NESINA, including inflammation of the pancreas (pancreatitis), which may be severe.

Certain medical conditions make you more likely to get pancreatitis.

Before you start taking NESINA:

Tell your doctor if you have ever had:

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- kidney problems
- liver problems

Stop taking NESINA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is NESINA?

- NESINA is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- NESINA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia). However, hypoglycemia may still occur with NESINA.
- NESINA is not for people with type 1 diabetes.
- NESINA is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if NESINA is safe and effective in children under the age of 18.

Who should not take NESINA?

Do not take NESINA if you:

- Are allergic to any ingredients in NESINA or have had a serious allergic (hypersensitivity) reaction to NESINA. See the end of this Medication Guide for a complete list of the ingredients in NESINA.
- Symptoms of a serious allergic reaction to NESINA may include:
 - swelling of your face, lips, throat and other areas on your skin
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - skin rash, itching, flaking or peeling

If you have any of these symptoms, stop taking NESINA and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with NESINA?

Before you take NESINA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have kidney or liver problems
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if NESINA can harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known whether NESINA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking NESINA

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start any new medicine.

NESINA may affect the way other medicines work, and other medicines may affect how NESINA works. Contact your doctor before you start or stop other types of medicines.

How should I take NESINA?

- Take NESINA exactly as your doctor tells you to take it.
- Take NESINA 1 time each day with or without food.

- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose, and take the next dose at your regular time. **Do not** take 2 doses of NESINA at the same time
- If you take too much NESINA, call your doctor or go to the nearest hospital emergency room right away
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to
- Your doctor may do certain blood tests before you start NESINA and during treatment as needed. Your doctor may change your dose of NESINA based on the results of your blood tests due to how well your kidneys are working
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C

What are the possible side effects of NESINA?

NESINA can cause serious side effects, including:

See “**What is the most important information I should know about NESINA?**”

- **Allergic (hypersensitivity) reactions** such as:
 - o swelling of your face, lips, throat and other areas on your skin
 - o difficulty with swallowing or breathing
 - o raised, red areas on your skin (hives)
 - o skin rash, itching, flaking or peeling

If you have these symptoms, stop taking NESINA and contact your doctor right away.

- **Liver problems.** Call your doctor right away if you have unexplained symptoms, such as:
 - o nausea or vomiting
 - o stomach pain
 - o unusual or unexplained tiredness
 - o loss of appetite
 - o dark urine
 - o yellowing of your skin or the whites of your eyes
- **Low blood sugar (hypoglycemia).** If you take NESINA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be

lowered while you take NESINA. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Signs and symptoms of low blood sugar include:

- | | |
|------------------------------|--------------------|
| o shaking or feeling jittery | o fast heartbeat |
| o sweating | o change in vision |
| o hunger | o confusion |
| o headache | o dizziness |
| o change in mood | |

The most common side effects of NESINA include:

- stuffy or runny nose and sore throat
- headache
- cold-like symptoms (upper respiratory tract infection)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NESINA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NESINA?

Store NESINA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep NESINA and all medicines out of the reach of children.

General information about the safe and effective use of NESINA

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take NESINA for a condition for which it was not prescribed. Do not give NESINA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about NESINA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about NESINA that is written for health professionals.

For more information go to www.NESINA.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in NESINA?

Active ingredient: alogliptin

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate. In addition, the film-coating contains the following inactive ingredients: hypromellose, titanium dioxide, ferric oxide (red or yellow) and polyethylene glycol and is marked with gray F1 printing ink

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

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NES011 R3

Medication Guide
JANUMET® XR (JAN-you-met XR)
(sitagliptin and metformin hydrochloride extended-release)
Tablets

Read this Medication Guide carefully before you start taking JANUMET XR and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JANUMET XR, ask your doctor or pharmacist.

What is the most important information I should know about JANUMET XR?

Serious side effects can happen in people taking JANUMET XR, including:

- 1. Lactic Acidosis.** Metformin, one of the medicines in JANUMET XR, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking JANUMET XR and call your doctor right away if you get any of the following symptoms, which could be signs of lactic acidosis.

You:

- feel very weak or tired.
- have unusual (not normal) muscle pain.
- have trouble breathing.
- have unusual sleepiness or sleep longer than usual.
- have sudden stomach or intestinal problems with nausea and vomiting or diarrhea.
- feel cold, especially in your arms and legs.
- feel dizzy or lightheaded.
- have a slow or irregular heartbeat.

You have a higher chance of getting lactic acidosis if you:

- have kidney problems. People whose kidneys are not working properly should not take JANUMET XR.
- have liver problems.
- have congestive heart failure that requires treatment with medicines.
- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking.
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have certain x-ray tests with dyes or contrast agents that are injected into your body.
- have surgery.
- have a heart attack, severe infection, or stroke.

- 2. Pancreatitis** (inflammation of the pancreas) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking JANUMET XR:

Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

Stop taking JANUMET XR and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JANUMET XR?

- JANUMET XR is a prescription medicine that contains 2 prescription diabetes medicines, sitagliptin (JANUVIA[®]) and extended-release metformin hydrochloride. JANUMET XR can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUMET XR is not for people with type 1 diabetes.
- JANUMET XR is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take JANUMET XR.
- It is not known if JANUMET XR is safe and effective when used in children under 18 years of age.

Who should not take JANUMET XR?

Do not take JANUMET XR if:

- your kidneys are not working properly.
- you are allergic to any of the ingredients in JANUMET XR. See the end of this Medication Guide for a complete list of ingredients in JANUMET XR.
Symptoms of a serious allergic reaction to JANUMET XR may include:
 - rash
 - raised red patches on your skin (hives)
 - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- you have diabetic ketoacidosis. See "**What is JANUMET XR?**".

What should I tell my doctor before taking JANUMET XR?

Before you take JANUMET XR, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
- are going to get an injection of dye or contrast agents for an x-ray procedure; JANUMET XR will need to be stopped for a short time. Talk to your doctor about when you should stop JANUMET XR and when you should start JANUMET XR again. See "**What is the most important information I should know about JANUMET XR?**".
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUMET XR will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.

Pregnancy Registry: If you take JANUMET XR at any time during your pregnancy, talk with your doctor about how you can join the JANUMET XR pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.

- are breast-feeding or plan to breast-feed. It is not known if JANUMET XR will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUMET XR.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. JANUMET XR may affect how well other drugs work and some drugs can affect how well JANUMET XR works.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take JANUMET XR?

- Take JANUMET XR exactly as your doctor tells you. Your doctor will tell you how many JANUMET XR tablets to take and when you should take them.
- Your doctor may change your dose of JANUMET XR if needed.
- Your doctor may tell you to take JANUMET XR along with certain other diabetes medicines. Low blood sugar (hypoglycemia) can happen more often when JANUMET XR is taken with certain other diabetes medicines. See **"What are the possible side effects of JANUMET XR?"**.
- Take JANUMET XR 1 time each day with a meal to help to lower your chance of having an upset stomach. It is better to take JANUMET XR with your evening meal.
- Take JANUMET XR tablets whole. Do not break, cut, crush, dissolve, or chew JANUMET XR tablets before swallowing. If you cannot swallow JANUMET XR tablets whole, tell your doctor.
- Continue to take JANUMET XR as long as your doctor tells you.
- If you take too much JANUMET XR, call your doctor or local Poison Control Center right away.
- If you miss a dose, take it with food as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of JANUMET XR at the same time.
- You may need to stop taking JANUMET XR for a short time. Call your doctor for instructions if you:
 - are dehydrated (have lost too much body fluid). Dehydration can occur if you are sick with severe vomiting, diarrhea or fever, or if you drink a lot less fluid than normal.
 - plan to have surgery.
 - are going to get an injection of dye or contrast agent for an x-ray procedure. See **"What is the most important information I should know about JANUMET XR?"** and **"What should I tell my doctor before taking JANUMET XR?"**.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these problems and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JANUMET XR.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JANUMET XR.

What are the possible side effects of JANUMET XR?

Serious side effects have happened in people taking JANUMET XR or the individual medicines in JANUMET XR.

- See **"What is the most important information I should know about JANUMET XR?"**.
- **Low blood sugar (hypoglycemia).** If you take JANUMET XR with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUMET XR. Signs and symptoms of low blood sugar may include:

- headache
 - drowsiness
 - weakness
 - dizziness
 - confusion
 - irritability
 - hunger
 - fast heart beat
 - sweating
 - feeling jittery
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUMET XR and call your doctor right away. See "**Who should not take JANUMET XR?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
 - **Kidney problems**, sometimes requiring dialysis.

The most common side effects of JANUMET XR include:

- stuffy or runny nose and sore throat
- upper respiratory infection
- diarrhea
- nausea and vomiting
- gas, upset stomach, indigestion
- weakness
- headache
- low blood sugar (hypoglycemia) when used in combination with certain medications, such as a sulfonylurea or insulin.

Taking JANUMET XR with meals can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unusual or sudden stomach problems, talk with your doctor. Stomach problems that start later during treatment may be a sign of something more serious.

JANUMET XR may have other side effects, including:

- swelling of the hands or legs. Swelling of the hands and legs can happen if you take JANUMET XR in combination with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.

These are not all the possible side effects of JANUMET XR. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual, or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JANUMET XR?

Store JANUMET XR at 68°F to 77°F (20°C to 25°C). Store in a dry place and keep cap tightly closed.

Keep JANUMET XR and all medicines out of the reach of children.

General information about the use of JANUMET XR.

Medicines are sometimes prescribed for purposes other than those listed in Medication Guides. Do not use JANUMET XR for a condition for which it was not prescribed. Do not give JANUMET XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JANUMET XR. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUMET XR that is written for health care professionals. For more information go to www.janumetxr.com or call 1-800-622-4477.

What are the ingredients in JANUMET XR?

Active ingredients: sitagliptin and metformin hydrochloride extended-release

Inactive ingredients:

- **All doses of JANUMET XR Tablets contain:** povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin. Film coating contains hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C #2/Indigo Carmine Aluminum Lake and carnauba wax.
- **In addition the JANUMET XR 50 mg/500 mg Tablets also contain:** microcrystalline cellulose.
- **In addition the JANUMET XR 50 mg/1000 mg Tablets also contain:** yellow iron oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Manufactured by:
Merck Sharp & Dohme Corp., a subsidiary of
Merck & Co., Inc., Whitehouse Station, NJ 08889, USA
OR
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US Patent Nos.: 6,699,871 and 7,326,708

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Medication Guide
JUVISYNC™ (JU-vih-sink)
(sitagliptin and simvastatin)
Tablets

Read this Medication Guide carefully before you start taking JUVISYNC and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JUVISYNC, ask your doctor or pharmacist.

What is the most important information I should know about JUVISYNC?

Serious side effects can happen in people taking JUVISYNC, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking JUVISYNC:

Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels
- kidney problems

Stop taking JUVISYNC and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JUVISYNC?

- JUVISYNC is a prescription medicine that contains two medicines, sitagliptin and simvastatin, in one pill. JUVISYNC can be used in adults who need both sitagliptin and simvastatin.
- Sitagliptin can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- Simvastatin can be used with diet and exercise in adults at high risk for heart attack or stroke to lower your chance of:
 - death from heart problems
 - having a heart attack or stroke
 - needing certain blood vessel procedures
- Simvastatin can be used in adults with certain cholesterol problems to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, simvastatin raises levels of HDL (good) cholesterol. Simvastatin is for people who cannot control their cholesterol levels by diet and exercise alone. You should stay on a cholesterol-lowering diet while taking this medicine.
- Sitagliptin is not for people with type 1 diabetes.
- Sitagliptin is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had inflammation of your pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take sitagliptin.
- JUVISYNC has not been studied in people who have an increase of chylomicrons (Fredrickson types I and V).
- JUVISYNC is not for people with certain kidney problems.
- It is not known if JUVISYNC is safe and effective when used in children under 18 years of age.

For more information, see the sections called "**What is type 2 diabetes?**" and "**What should I know about high cholesterol?**".

Who should not take JUVISYNC?

Do not take JUVISYNC if you:

- are allergic to any of the ingredients in JUVISYNC. See the end of this Medication Guide for a complete list of ingredients in JUVISYNC.

Symptoms of a serious allergic reaction to JUVISYNC may include:

- rash
- raised red patches on your skin (hives)
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- take certain medicines such as:
 - anti-fungal medicines including:
 - itraconazole
 - ketoconazole
 - posaconazole
 - voriconazole
 - HIV protease inhibitors, including:
 - indinavir
 - nelfinavir
 - ritonavir
 - saquinavir
 - tipranavir
 - atazanavir
 - certain hepatitis C virus protease inhibitors, including:
 - boceprevir
 - telaprevir
 - certain antibiotics, including:
 - erythromycin
 - clarithromycin
 - telithromycin
 - nefazodone
 - a fibrate medicine for lowering cholesterol called gemfibrozil
 - cyclosporine
 - danazol

Ask your doctor if you are not sure whether your medicine is listed above.

- have active liver disease or repeated blood tests indicating possible liver problems.
- are pregnant or think you may be pregnant, or you are planning to become pregnant.
- are a woman of childbearing age, you should use an effective method of birth control to prevent pregnancy while using JUVISYNC.
- are breastfeeding or plan to breastfeed.

What should I tell my doctor before taking JUVISYNC?

Before you take JUVISYNC, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.

- drink substantial quantities of alcohol or ever had liver problems.
- have any other medical conditions.
- are taking drugs that prevent blood clots, such as warfarin.

Taking JUVISYNC with certain substances can increase the risk of muscle problems. It is especially important to tell your doctor if you take:

- fibric acid derivatives (such as fenofibrate)
- amiodarone or dronedarone (drugs used to treat an irregular heartbeat)
- the following medicines used to treat high blood pressure, chest pain with heart disease, or other heart problems:
 - verapamil
 - diltiazem
 - amlodipine
 - ranolazine
- grapefruit juice (which should be avoided while taking JUVISYNC)
- colchicine (a medicine used to treat gout)
- large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product, as this may increase your risk of muscle problems, especially if you are Chinese.

Tell all of your doctors about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take JUVISYNC?

- Take one JUVISYNC tablet each day, in the evening, exactly as your doctor tells you.
- Do not break or cut JUVISYNC tablets before swallowing. If you cannot swallow JUVISYNC tablets whole, tell your doctor.
- Your doctor may tell you to take JUVISYNC along with other diabetes medicines. Low blood sugar can happen more often when JUVISYNC is taken with certain other diabetes medicines. See **"What are the possible side effects of JUVISYNC?"**.
- If you take too much JUVISYNC, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JUVISYNC.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will monitor your condition with regular blood tests, including your blood sugar levels, hemoglobin A1C, and cholesterol levels, and to check for side effects.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JUVISYNC. Your doctor may change your dose or discontinue JUVISYNC based on the results of your blood tests.

What are the possible side effects of JUVISYNC?

Serious side effects have happened in people taking JUVISYNC.

- See "**What is the most important information I should know about JUVISYNC?**".
- **myopathy (muscle weakness) and rhabdomyolysis (muscle breakdown).** Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness especially with fever while you take JUVISYNC.
 - Muscle problems, including muscle breakdown, can be serious in some people and on rare occasions may cause kidney damage that can lead to death.
 - The risk of muscle breakdown is greater at higher doses of JUVISYNC.
 - The risk of muscle breakdown is greater in people 65 years of age and older, females, and people with kidney or thyroid problems.

If you have muscle problems that do not go away even after your doctor has advised you to stop taking JUVISYNC, notify your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.

- **liver problems.** Your doctor should do blood tests to check your liver before you start taking JUVISYNC and if you have any symptoms of liver problems while you take JUVISYNC. Call your doctor right away if you have the following symptoms of liver problems:
 - feel tired or weak
 - loss of appetite
 - upper belly pain
 - dark urine
 - yellowing of your skin or the whites of your eyes
- **kidney problems**, sometimes requiring dialysis
- **low blood sugar (hypoglycemia).** If you take JUVISYNC with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JUVISYNC. Signs and symptoms of low blood sugar may include:

• headache	• irritability
• drowsiness	• hunger
• weakness	• fast heart beat
• dizziness	• sweating
• confusion	• feeling jittery
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JUVISYNC and call your doctor right away. See "**Who should not take JUVISYNC?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

The most common side effects of JUVISYNC include:

- upper respiratory infection
- stuffy or runny nose and sore throat
- headache
- stomach pain
- constipation
- nausea

JUVISYNC may have other side effects, including:

- swelling of the hands or legs. Swelling of the hands or legs can happen if you take JUVISYNC in combination with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.
- joint pain
- muscle pain
- alterations in some laboratory blood tests
- liver problems (sometimes serious)
- nausea
- dizziness
- tingling sensation
- depression
- trouble sleeping
- poor memory
- erectile dysfunction
- breathing problems including persistent cough and/or shortness of breath or fever.

These are not all the possible side effects of JUVISYNC. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JUVISYNC?

Store JUVISYNC at 68°F to 77°F (20°C to 25°C). Store in a dry place with cap tightly closed.

Keep JUVISYNC and all medicines out of the reach of children.

General information about the use of JUVISYNC

Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JUVISYNC for a condition for which it was not prescribed. Do not give JUVISYNC to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JUVISYNC. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JUVISYNC that is written for health professionals. For more information, go to www.JUVISYNC.com or call 1-800-622-4477.

What are the ingredients in JUVISYNC?

Active ingredients: sitagliptin and simvastatin

Inactive ingredients: anhydrous dibasic calcium phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose monohydrate, pre-gelatinized corn starch, butylated hydroxyanisole. The tablet film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and red iron oxide. The film coating for certain tablet strengths also contains yellow iron oxide and black iron oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque, which can slow or block blood flow to your heart, brain, and other organs.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.



Manufactured by:
MSD International GmbH
Clonmel, Co. Tipperary,
Ireland

US Patent Nos.: 6,699,871 and 7,326,708

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

MEDICATION GUIDE $\mathcal{R}$ ONLY
KOMBIGLYZE XR (kom-be-glyze X-R)
(saxagliptin and metformin HCl extended-release) tablets

Read this Medication Guide carefully before you start taking KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have any questions about KOMBIGLYZE XR, ask your healthcare provider.

What is the most important information I should know about KOMBIGLYZE XR?

Serious side effects can happen in people taking KOMBIGLYZE XR, including:

1. **Lactic Acidosis.** Metformin hydrochloride, one of the medicines in KOMBIGLYZE XR, can cause a rare, but serious, side effect called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital.

Stop taking KOMBIGLYZE XR and call your healthcare provider right away if you get any of the following symptoms of lactic acidosis:

- feel very weak and tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have unusual sleepiness or sleep longer than usual
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis if you:

- have kidney problems. People whose kidneys are not working properly should not take KOMBIGLYZE XR.
- have liver problems.
- have congestive heart failure that requires treatment with medicines.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

- drink a lot of alcohol (very often or short-term “binge” drinking).
 - get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
 - have certain x-ray tests with injectable dyes or contrast agents.
 - have surgery.
 - have a heart attack, severe infection, or stroke.
 - are 80 years of age or older and have not had your kidney function tested.
2. **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking KOMBIGLYZE XR:

Tell your healthcare provider if you have ever had

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with KOMBIGLYZE XR.

Stop taking KOMBIGLYZE XR and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is KOMBIGLYZE XR?

- KOMBIGLYZE XR is a prescription medicine that contains saxagliptin and metformin hydrochloride. KOMBIGLYZE XR is used with diet and exercise to help control high blood sugar (hyperglycemia) in adults with type 2 diabetes.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

- KOMBIGLYZE XR is not for people with type 1 diabetes.
- KOMBIGLYZE XR is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had inflammation of the pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take KOMBIGLYZE XR.

It is not known if KOMBIGLYZE XR is safe and effective in children younger than 18 years old.

Who should not take KOMBIGLYZE XR?

Do not take KOMBIGLYZE XR if you:

- have kidney problems.
- are allergic to metformin hydrochloride, saxagliptin, or any of the ingredients in KOMBIGLYZE XR. See the end of this Medication Guide for a complete list of ingredients in KOMBIGLYZE XR.

Symptoms of a serious allergic reaction to KOMBIGLYZE XR may include:

- swelling of your face, lips, throat, and other areas on your skin
- difficulty with swallowing or breathing
- raised, red areas on your skin (hives)
- skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking KOMBIGLYZE XR and contact your healthcare provider right away.

- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

What should I tell my healthcare provider before taking KOMBIGLYZE XR?

Before you take KOMBIGLYZE XR, tell your healthcare provider if you:

- have type 1 diabetes. KOMBIGLYZE XR should not be used to treat type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). KOMBIGLYZE XR should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

- have liver problems.
- have heart problems, including congestive heart failure.
- are older than 80 years. If you are over 80 years old you should not take KOMBIGLYZE XR unless your kidneys have been checked and they are normal.
- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking.
- are going to get an injection of dye or contrast agents for an x-ray procedure or if you are going to have surgery and will not be able to eat or drink much. In these situations, KOMBIGLYZE XR will need to be stopped for a short time. Talk to your healthcare provider about when you should stop KOMBIGLYZE XR and when you should start KOMBIGLYZE XR again. See “**What is the most important information I should know about KOMBIGLYZE XR?**”
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if KOMBIGLYZE XR will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. It is not known if KOMBIGLYZE XR passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you take KOMBIGLYZE XR.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

KOMBIGLYZE XR may affect the way other medicines work, and other medicines may affect how KOMBIGLYZE XR works.

Tell your healthcare provider if you will be starting or stopping certain other types of medicines, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of KOMBIGLYZE XR might need to be changed.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

How should I take KOMBIGLYZE XR?

- Take KOMBIGLYZE XR exactly as your healthcare provider tells you.
- KOMBIGLYZE XR should be taken with meals to help lessen an upset stomach side effect.
- Swallow KOMBIGLYZE XR whole. Do not crush, cut, or chew KOMBIGLYZE XR.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like KOMBIGLYZE XR tablets.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your healthcare provider right away if you have any of these problems.
- Your healthcare provider should do blood tests to check how well your kidneys are working before and during your treatment with KOMBIGLYZE XR.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you. See **"What are the possible side effects of KOMBIGLYZE XR?"**
- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while taking KOMBIGLYZE XR.
- If you miss a dose of KOMBIGLYZE XR, take your next dose as prescribed unless your healthcare provider tells you differently. Do not take an extra dose the next day.
- If you take too much KOMBIGLYZE XR, call your healthcare provider, local Poison Control Center, or go to the nearest hospital emergency room right away.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

What are the possible side effects of KOMBIGLYZE XR?

KOMBIGLYZE XR can cause serious side effects, including:

- See **"What is the most important information I should know about KOMBIGLYZE XR?"**
- **Allergic (hypersensitivity) reactions**, such as:
 - swelling of your face, lips, throat, and other areas on your skin
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking KOMBIGLYZE XR and contact your healthcare provider right away.

Low blood sugar (hypoglycemia) may become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Common side effects of KOMBIGLYZE XR include:

- upper respiratory tract infection
- stuffy or runny nose and sore throat
- urinary tract infection
- headache
- diarrhea
- nausea and vomiting

Taking KOMBIGLYZE XR with meals can help lessen the common stomach side effects of metformin. If you have unexplained stomach problems, tell your healthcare provider. Stomach problems that start later during treatment may be a sign of something more serious.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

Tell your healthcare provider if you have any side effects that bother you or that do not go away.

These are not all of the possible side effects of KOMBIGLYZE XR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store KOMBIGLYZE XR?

Store KOMBIGLYZE XR between 68°F and 77°F (20°C and 25°C).

Keep KOMBIGLYZE XR and all medicines out of the reach of children.

General information about the use of KOMBIGLYZE XR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KOMBIGLYZE XR for a condition for which it was not prescribed. Do not give KOMBIGLYZE XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about KOMBIGLYZE XR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about KOMBIGLYZE XR that is written for healthcare professionals.

For more information, go to www.kombiglyzexr.com or call 1-800-664-5992.

What are the ingredients of KOMBIGLYZE XR?

Active ingredients: saxagliptin and metformin hydrochloride.

Inactive ingredients in each tablet: carboxymethyl-cellulose sodium, hypromellose 2208, and magnesium stearate.

The 5 mg/500 mg tablet also contains: micro-crystalline cellulose and hypromellose 2910.

Tablet film coat contains: polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, and iron oxides.

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release)

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

Talk to your healthcare provider about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets

Manufactured by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:

Bristol-Myers Squibb Company
Princeton, NJ 08543

and

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850



Bristol-Myers Squibb

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JENTADUETO safely and effectively. See full prescribing information for JENTADUETO.

Jentadueto® (linagliptin and metformin hydrochloride) tablets
Initial U.S. Approval: 2012

WARNING: RISK OF LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue JENTADUETO and hospitalize the patient immediately (5.1)**

RECENT MAJOR CHANGES

Indications and Usage

Important Limitations of Use (1.2) 6/2013

Dosage and Administration

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin (2.2) 9/2013

Warnings and Precautions

Pancreatitis (5.2) 6/2013

Use with Medications Known to Cause Hypoglycemia (5.5) 9/2013

INDICATIONS AND USAGE

JENTADUETO is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate (1.1)

Important limitations of use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis (1.2)
- Has not been studied in patients with a history of pancreatitis (1.2)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of JENTADUETO based on the patient's current regimen (2.1)
- The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin twice daily (2.1)
- Should be given twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

2.5 mg linagliptin/500 mg metformin hydrochloride

2.5 mg linagliptin/850 mg metformin hydrochloride

2.5 mg linagliptin/1000 mg metformin hydrochloride (3)

CONTRAINDICATIONS

- Renal impairment (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- Hypersensitivity to linagliptin or metformin (4)

WARNINGS AND PRECAUTIONS

- **Lactic acidosis:** Warn against excessive alcohol use. JENTADUETO is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.1, 5.3, 5.4, 5.7, 5.8)
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue JENTADUETO. (5.2)
- Temporarily discontinue JENTADUETO in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids (5.3)
- **Hypoglycemia:** When used with an insulin secretagogue (e.g., sulfonylurea (SU) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (2.2, 5.5)
- **Vitamin B₁₂ deficiency:** Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.6)
- **Macrovascular outcomes:** No conclusive evidence of macrovascular risk reduction with JENTADUETO or any other antidiabetic drug (5.9)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with JENTADUETO and more commonly than in patients treated with placebo are nasopharyngitis and diarrhea (6.1)
- Hypoglycemia was more commonly reported in patients treated with the combination of JENTADUETO and SU compared with those treated with the combination of SU and metformin (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cationic drugs eliminated by renal tubular secretion: May reduce metformin elimination. Use with caution. (7.1)
- P-glycoprotein/CYP3A4 inducer: The efficacy of JENTADUETO may be reduced when administered in combination (e.g., rifampin). Use of alternative treatments is strongly recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are no adequate and well-controlled studies in pregnant women. JENTADUETO tablets should be used during pregnancy only if clearly needed. (8.1)
- **Nursing mothers:** Caution should be exercised when JENTADUETO is administered to a nursing woman (8.3)
- **Pediatric patients:** Safety and effectiveness of JENTADUETO in patients below the age of 18 have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2013

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JENTADUETO should be discontinued and the patient hospitalized immediately [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

1.1 Indication

JENTADUETO tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate [see Dosage and Administration (2.1) and Clinical Studies (14.1)].

1.2 Important Limitations of Use

JENTADUETO should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

JENTADUETO has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using JENTADUETO [see Warnings and Precautions (5.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of JENTADUETO should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. JENTADUETO should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. For available dosage forms and strengths see [Dosage Forms and Strengths (3)].

Recommended starting dose:

- In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily
- In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals).
- Patients already treated with linagliptin and metformin individual components may be switched to JENTADUETO containing the same doses of each component.

No studies have been performed specifically examining the safety and efficacy of JENTADUETO in patients previously treated with other oral antihyperglycemic agents and switched to JENTADUETO. Any change in therapy of type 2 diabetes mellitus should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

2.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When JENTADUETO is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia [see Warnings and Precautions (5.5)].

3 DOSAGE FORMS AND STRENGTHS

JENTADUETO is a combination of linagliptin and metformin hydrochloride. JENTADUETO tablets are available in the following dosage forms and strengths:

- 2.5 mg linagliptin/500 mg metformin hydrochloride tablets are light yellow, oval, biconvex tablets debossed with “D2/500” on one side and the Boehringer Ingelheim logo on the other side
- 2.5 mg linagliptin/850 mg metformin hydrochloride tablets are light orange, oval, biconvex tablets debossed with “D2/850” on one side and the Boehringer Ingelheim logo on the other side
- 2.5 mg linagliptin/1000 mg metformin hydrochloride tablets are light pink, oval, biconvex tablets debossed with “D2/1000” on one side and the Boehringer Ingelheim logo on the other side

4 CONTRAINDICATIONS

JENTADUETO is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [see Warnings and Precautions (5.1, 5.3)]
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin [see Warnings and Precautions (5.1)]
- A history of hypersensitivity reaction to linagliptin (such as urticaria, angioedema, or bronchial hyperreactivity) or metformin [see Adverse Reactions (6.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JENTADUETO and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of >5 $\mu\text{g/mL}$ are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple

concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

The onset of lactic acidosis is often subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. More severe acidosis may be associated with signs such as hypothermia, hypotension, and resistant bradyarrhythmias. Patients should be educated to recognize and promptly report these symptoms. If present, JENTADUETO should be discontinued until lactic acidosis is ruled out. Gastrointestinal symptoms, which are commonly reported during initiation of metformin therapy are less frequently observed in subjects on a chronic, stable, dose of metformin. Gastrointestinal symptoms in subjects on chronic, stable, dose of metformin could be caused by lactic acidosis or other serious disease.

To rule out lactic acidosis, serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be due to other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and supportive measures promptly instituted. Metformin is dialyzable (clearance of up to 170 mL/min under good hemodynamic conditions) and prompt hemodialysis is recommended to remove the accumulated metformin and correct the metabolic acidosis. Such management often results in prompt reversal of symptoms and recovery [see *Boxed Warning*].

5.2 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JENTADUETO and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JENTADUETO.

5.3 Monitoring of Renal Function

Although linagliptin undergoes minimal renal excretion, metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, JENTADUETO is contraindicated in patients with renal impairment.

Before initiation of therapy with JENTADUETO and at least annually thereafter, renal function should be assessed and verified to be normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and JENTADUETO discontinued if evidence of renal impairment is present.

Linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg if JENTADUETO is discontinued due to evidence of renal impairment. No dose adjustment of linagliptin is recommended in patients with renal impairment.

Use of concomitant medications that may affect renal function or metformin disposition:

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

Radiological studies and surgical procedures:

Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, JENTADUETO should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been confirmed to be normal.

JENTADUETO should be temporarily discontinued for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

5.4 Impaired Hepatic Function

Because impaired hepatic function has been associated with some cases of lactic acidosis with metformin therapy, JENTADUETO should generally be avoided in patients with clinical or laboratory evidence of hepatic disease [see *Warnings and Precautions (5.1)*].

5.5 Use with Medications Known to Cause Hypoglycemia

Linagliptin

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial [see *Adverse Reactions (6.1)*]. The use of linagliptin in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JENTADUETO [see *Dosage and Administration (2.2)*].

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β -adrenergic blocking drugs.

5.6 Vitamin B₁₂ Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B₁₂ levels appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JENTADUETO and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurement at 2- to 3-year intervals may be useful.

5.7 Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving JENTADUETO [see Warnings and Precautions (5.1)].

5.8 Hypoxic States

Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JENTADUETO therapy, the drug should be promptly discontinued [see Warnings and Precautions (5.1)].

5.9 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with linagliptin or metformin or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Linagliptin/Metformin

The safety of concomitantly administered linagliptin (daily dose 5 mg) and metformin (mean daily dose of approximately 1800 mg) has been evaluated in 2816 patients with type 2 diabetes mellitus treated for ≥12 weeks in clinical trials.

Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse events which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%).

In a 24-week factorial design study, adverse events reported in ≥5% of patients receiving linagliptin + metformin and were more common than in patients given placebo are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Linagliptin + Metformin and Greater than with Placebo in a 24-week Factorial-Design Study

	Placebo n=72	Linagliptin Monotherapy n=142	Metformin Monotherapy n=291	Combination of Linagliptin with Metformin n=286
	n (%)	n (%)	n (%)	n (%)
Nasopharyngitis	1 (1.4)	8 (5.6)	8 (2.7)	18 (6.3)
Diarrhea	2 (2.8)	5 (3.5)	11 (3.8)	18 (6.3)

Other adverse reactions reported in clinical studies with treatment of linagliptin + metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperreactivity), cough, decreased appetite, nausea, vomiting, pruritus, and pancreatitis.

Linagliptin

Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% vs 6.1%), diarrhea (3.3% vs 3.0%), and cough (2.1% vs 1.4%).

Rates for other adverse reactions for linagliptin 5 mg vs placebo when linagliptin was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when linagliptin was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when linagliptin was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when linagliptin was used as add-on to basal insulin therapy.

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Metformin

The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anemia) [see Warnings and Precautions (5.5)].

Hypoglycemia

Linagliptin/Metformin

In a 24-week factorial design study, hypoglycemia was reported in 4 (1.4%) of 286 subjects treated with linagliptin + metformin, 6 (2.1%) of 291 subjects treated with metformin, and 1 (1.4%) of 72 subjects treated with placebo. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 (22.9%) of 792 patients reported hypoglycemia compared with 39 (14.8%) of 263 patients administered placebo in combination with metformin and sulfonylurea. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

Linagliptin

In the study of patients receiving linagliptin as add-on therapy to a stable dose of insulin for up to 52 weeks (n=1261), no significant difference in the incidence of investigator reported hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self measured blood glucose ≤ 70 mg/dL, was noted between the linagliptin- (31.4%) and placebo- (32.9%) treated groups.

Use in Renal Impairment

Linagliptin was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 133 patients with severe renal impairment (estimated GFR < 30 mL/min). For the initial 12 weeks of the study, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dose adjustments in antidiabetic background therapy were allowed.

In general, the incidence of adverse events including severe hypoglycemia was similar to those reported in other linagliptin trials. The observed incidence of hypoglycemia was higher (linagliptin, 63% compared to placebo, 49%) due to an increase in asymptomatic hypoglycemic events especially during the first 12 weeks when background glycemic therapies were kept stable. Ten linagliptin-treated patients (15%) and 11 placebo-treated patients (17%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying finger stick glucose ≤ 54 mg/dL). During the same time period, severe hypoglycemic events, defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 3 (4.4%) linagliptin-treated patients and 3 (4.6%) placebo-treated patients. Events that were considered life-threatening or required hospitalization were reported in 2 (2.9%) patients on linagliptin and 1 (1.5%) patient on placebo.

Renal function as measured by mean eGFR and creatinine clearance did not change over 52 weeks' treatment compared to placebo.

Laboratory Tests

Changes in laboratory findings were similar in patients treated with linagliptin + metformin compared to patients treated with placebo + metformin. Changes in laboratory values that occurred more frequently in the linagliptin + metformin group and $\geq 1\%$ more than in the placebo group were not detected.

No clinically meaningful changes in vital signs were observed in patients treated with linagliptin.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of linagliptin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Acute pancreatitis, including fatal pancreatitis [see *Indications and Usage (1.2)* and *Warnings and Precautions (5.2)*]
- Rash

7 DRUG INTERACTIONS

7.1 Drug Interactions with Metformin

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JENTADUETO and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JENTADUETO, as the risk of lactic acidosis may increase [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.2 Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As JENTADUETO is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary [see *Clinical Pharmacology (12.3)*].

7.3 Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JENTADUETO, the patient should be closely observed to maintain adequate glycemic control [see *Clinical Pharmacology (12.3)*]. When such drugs are withdrawn from a patient receiving JENTADUETO, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

JENTADUETO

There are no adequate and well controlled studies in pregnant women with JENTADUETO or its individual components, and some clinical data is available for metformin which indicate that the risk for major malformations was not increased when metformin is taken during the first trimester in pregnancy. In addition, metformin was not associated with increased perinatal complications. Nevertheless, because these clinical data cannot rule out the possibility of harm, JENTADUETO should be used during pregnancy only if clearly needed.

JENTADUETO was not teratogenic when administered to Wistar Han rats during the period of organogenesis at doses similar to clinical exposure. At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations.

Linagliptin

Linagliptin was not teratogenic when administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times the clinical dose in rats and 1943 times the clinical dose in rabbits, based on exposure. No functional, behavioral, or reproductive toxicity was observed in offspring of female Wistar Han rats when administered linagliptin from gestation day 6 to lactation day 21 at a dose 49 times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

Metformin Hydrochloride

Metformin has been studied for embryofetal effects in 2 rat strains and in rabbits. Metformin was not teratogenic in Sprague Dawley rats up to 600 mg/kg or in Wistar Han rats up to 200 mg/kg (2-3 times the clinical dose based on body surface area or exposure, respectively). At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), an increased incidence of rib and scapula skeletal malformations was observed in the Wistar Han strain. Metformin was not teratogenic in rabbits at doses up to 140 mg/kg (similar to clinical dose based on body surface area).

Metformin administered to female Sprague Dawley rats from gestation day 6 to lactation day 21 up to 600 mg/kg/day (2 times the maximum clinical dose based on body surface area) had no effect on prenatal or postnatal development of offspring.

Metformin crosses the placenta into the fetus in rats and humans.

8.3 Nursing Mothers

No studies in lactating animals have been conducted with the combined components of JENTADUETO. In studies performed with the individual components, both linagliptin and metformin were secreted in the milk of lactating rats. It is not known whether linagliptin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of JENTADUETO in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney. Considering that aging can be associated with reduced renal function, JENTADUETO should be used with caution as age increases [see *Warnings and Precautions* (5.1, 5.3) and *Clinical Pharmacology* (12.3)].

Linagliptin

There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) patients were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see *Contraindications* (4), *Warnings and Precautions* (5.3), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

In the event of an overdose with JENTADUETO, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom JENTADUETO overdose is suspected.

Linagliptin

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of linagliptin (equivalent to 120 times the recommended daily dose), there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Boxed Warning and Warnings and Precautions* (5.1)].

11 DESCRIPTION

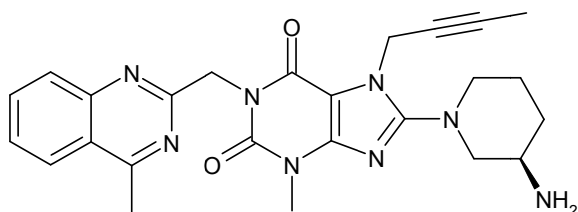
JENTADUETO tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus: linagliptin and metformin hydrochloride.

Linagliptin

Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

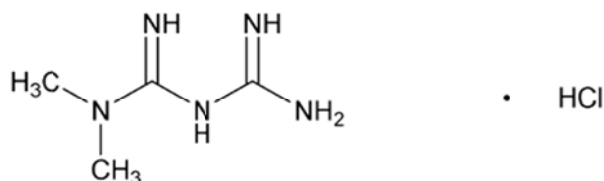
The empirical formula is C₂₅H₂₈N₈O₂ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Metformin Hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



JENTADUETO

JENTADUETO is available for oral administration as tablets containing 2.5 mg linagliptin and 500 mg metformin hydrochloride (JENTADUETO 2.5 mg/500 mg), 850 mg metformin hydrochloride (JENTADUETO 2.5 mg/850 mg) or 1000 mg metformin hydrochloride (JENTADUETO 2.5 mg/1000 mg). Each film-coated tablet of JENTADUETO contains the following inactive ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JENTADUETO

JENTADUETO combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) [see *Warnings and Precautions* (5.9)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

JENTADUETO

The results of a bioequivalence study in healthy subjects demonstrated that JENTADUETO (linagliptin/metformin hydrochloride) 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of linagliptin and metformin as individual tablets. Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg fixed-dose combination with food resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC; however, mean peak serum concentration of metformin was decreased by 18% when administered with food. A delayed time-to-peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.

Absorption

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Linagliptin

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Linagliptin

Following administration of an oral [14 C]linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

JENTADUETO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO in renally impaired patients have not been performed. Since metformin is contraindicated in patients with renal impairment, use of JENTADUETO is also contraindicated in patients with renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL [males] or ≥ 1.4 mg/dL [females], or abnormal creatinine clearance) [see *Contraindications (4) and Warnings and Precautions (5.3)*].

Linagliptin: Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function.

Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in AUC by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

Metformin: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance [see *Contraindications (4) and Warnings and Precautions (5.3)*].

Hepatic Impairment

JENTADUETO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO in hepatically impaired patients have not been performed. However, use of metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use of JENTADUETO is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.4)*].

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Body Mass Index (BMI)/Weight

Linagliptin: BMI/Weight had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Gender

Linagliptin: Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

Geriatric

JENTADUETO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO in geriatric patients have not been performed. Based on the metformin component, JENTADUETO treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced [see *Warnings and Precautions* (5.1, 5.3) and *Use in Specific Populations* (8.5)].

Linagliptin: Age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO in pediatric patients have not yet been performed.

Race

Linagliptin: Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic data, including subjects of White, Hispanic, Black, and Asian racial groups.

Metformin hydrochloride: No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Drug Interactions

Pharmacokinetic drug interaction studies with JENTADUETO have not been performed; however, such studies have been conducted with the individual components of JENTADUETO (linagliptin and metformin hydrochloride).

Linagliptin

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp, and OCT. No dose adjustment of linagliptin is recommended based on results of the described pharmacokinetic studies.

Table 2 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0	
			AUC [†]	C _{max}
No dosing adjustments required for linagliptin when given with the following coadministered drugs:				
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg [#]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg [#]	2.01	2.96
The efficacy of JENTADUETO may be reduced when administered in combination with strong inducers of CYP3A4 or P-gp (e.g., rifampin). Use of alternative treatments is strongly recommended [see Drug Interactions (7.2)].				
Rifampin	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady state) unless otherwise noted

[#] Single dose

[†]AUC = AUC(0 to 24 hours) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments

QD = once daily

BID = twice daily

TID = three times daily

Table 3 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg [#]	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg [#]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

* Multiple dose (steady state) unless otherwise noted

[#] Single dose[†]AUC = AUC(INF) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments**AUC=AUC(0-168) and C_{max}=E_{max} for pharmacodynamic end points

INR = International Normalized Ratio

PT = Prothrombin Time

QD = once daily

TID = three times daily

Metformin hydrochloride

Table 4 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution [see Warnings and Precautions (5.3) and Drug Interactions (7.1)].					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses

[†] AUC = AUC(INF)[‡] Ratio of arithmetic means

**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 5 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶

* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF) unless otherwise noted

‡ Ratio of arithmetic means, p-value of difference <0.05

§ AUC(0-24 hr) reported

¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JENTADUETO

No animal studies have been conducted with the combined products in JENTADUETO to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with JENTADUETO.

The following data are based on the findings in studies with linagliptin and metformin individually.

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35 and 270 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215 times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

14 CLINICAL STUDIES

The coadministration of linagliptin and metformin has been studied in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise and in combination with sulfonylurea.

There have been no clinical efficacy studies conducted with JENTADUETO; however, bioequivalence of JENTADUETO to linagliptin and metformin coadministered as individual tablets was demonstrated in healthy subjects.

14.1 Initial Combination Therapy with Metformin

A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial study designed to assess the efficacy of linagliptin as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control (A1C $\geq 7.0\%$ to $\leq 10.5\%$) were randomized. Patients with inadequate glycemic control (A1C $\geq 7.5\%$ to $< 11.0\%$) not on antihyperglycemic agents at study entry (48%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Randomization was stratified by baseline A1C ($< 8.5\%$ vs $\geq 8.5\%$) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of linagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C, and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 6, Figure 1). The adjusted mean treatment difference in A1C from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to metformin 1000 mg twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to linagliptin 5 mg once daily; -0.6% (95% CI -0.8, -0.4; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to linagliptin 5 mg once daily.

Lipid effects were generally neutral. No meaningful change in body weight was noted in any of the 6 treatment groups.

Table 6 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	Linagliptin 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily
A1C (%)						
Number of patients	n=65	n=135	n=141	n=137	n=138	n=140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n=61	n=134	n=136	n=135	n=132	n=136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

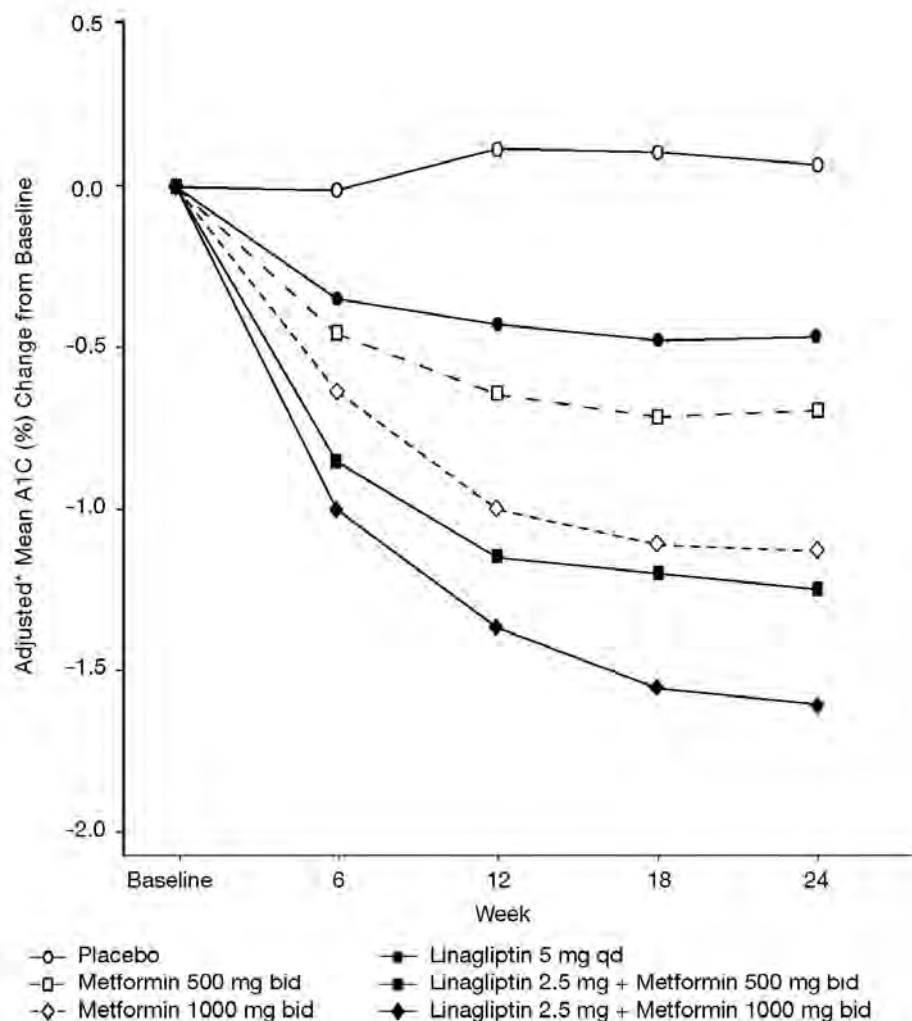
*Total daily dose of linagliptin is equal to 5 mg

**Full analysis population using last observation on study

***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily, n=138.

****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Figure 1 Adjusted Mean Change from Baseline for A1C (%) over 24 Weeks with Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise - FAS completers.



*Variables used in adjustment: Baseline A1C and prior use of OADs

14.2 Add-On Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with metformin. Patients already on metformin (n=491) at a dose of at least 1500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n=207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either linagliptin 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, linagliptin provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 7). Rescue glycemic therapy was used in 7.8% of patients treated with linagliptin 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 7 Glycemic Parameters in Placebo-Controlled Study for Linagliptin in Combination with Metformin*

	Linagliptin 5 mg + Metformin	Placebo + Metformin
A1C (%)		
Number of patients	n=513	n=175
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean***)	-0.5	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	--
Patients [n (%)] achieving A1C <7%**	127 (26.2)	15 (9.2)
FPG (mg/dL)		
Number of patients	n=495	n=159
Baseline (mean)	169	164
Change from baseline (adjusted mean***)	-11	11
Difference from placebo + metformin (adjusted mean) (95% CI)	-21 (-27, -15)	--
2-hour PPG (mg/dL)		
Number of patients	n=78	n=21
Baseline (mean)	270	274
Change from baseline (adjusted mean***)	-49	18
Difference from placebo + metformin (adjusted mean) (95% CI)	-67 (-95, -40)	--

* Full analysis population using last observation on study

**Linagliptin 5 mg + Metformin, n=485; Placebo + Metformin, n=163.

***HbA1c: ANCOVA model included treatment and number of prior oral OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

14.3 Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of linagliptin was evaluated in a 104-week double-blind, glimepiride-controlled non-inferiority study in type 2 diabetic patients with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dose of ≥ 1500 mg per day) and washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of linagliptin 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs $\geq 8.5\%$), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dose of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 weeks and 104 weeks, linagliptin and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for linagliptin, -0.6% for glimepiride; 104 weeks: -0.2% for TRADJENTA, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 8). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 8 Glycemic Parameters at 52 and 104 Weeks in Study Comparing Linagliptin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	Linagliptin 5 mg + Metformin	Glimepiride + Metformin (mean glimepiride dose 3 mg)	TRADJENTA 5 mg + Metformin	Glimepiride + Metformin (mean glimepiride dose 3 mg)
A1C (%)				
Number of patients	n=764	n=755	n=764	n=755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean****)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n=733	n=725	n=733	n=725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean****)	8*	-15	-2 [†]	-9
Hypoglycemia incidence (%)***				
Number of patients	n=776	n=775	n=776	n=775
Incidence	5.3*	31.1	7.5 *	36.1

*p<0.0001 vs glimepiride; [†]p=0.0012 vs glimepiride

**Full analysis population using last observation on study

***Hypoglycemic incidence included both asymptomatic events (not accompanied by typical symptoms and plasma glucose concentration of ≤ 70 mg/dL) and symptomatic events with typical symptoms of hypoglycemia and plasma glucose concentration of ≤ 70 mg/dL.

****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. Hypoglycemia incidence (%): Cochran-Mantel-Haenszel test was performed on the patient population contained in the treated set, to compare the proportion of patients with hypoglycemic events between patients treated with linagliptin and patients treated with glimepiride.

Patients treated with linagliptin had a mean baseline body weight of 86 kg and were observed to have an adjusted mean decrease in body weight of 1.1 kg at 52 weeks and 1.4 kg at 104 weeks. Patients on glimepiride had a mean baseline body weight of 87 kg and were observed to have an adjusted mean increase from baseline in body weight of 1.4 kg at 52 weeks and 1.3 kg at 104 weeks (treatment difference p<0.0001 for both timepoints).

14.4 Add-On Combination Therapy with Metformin and a Sulfonylurea

A total of 1058 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the study were glimepiride (31%), glibenclamide (26%), and gliclazide (26% [not available in the United States]). Patients on a sulfonylurea and metformin were randomized to receive linagliptin 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue. Glycemic end points measured included A1C and FPG.

In combination with a sulfonylurea and metformin, linagliptin provided statistically significant improvements in A1C and FPG compared with placebo (Table 9). In the entire study population (patients on linagliptin in combination with a sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with linagliptin 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 9 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin in Combination with Metformin and Sulfonylurea*

	Linagliptin 5 mg + Metformin + SU	Placebo + Metformin + SU
A1C (%)		
Number of patients	n=778	n=262
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean***)	-0.7	-0.1
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.7, -0.5)	--
Patients [n (%)] achieving A1C <7%**	217 (29.2)	20 (8.1)
FPG (mg/dL)		
Number of patients	n=739	n=248
Baseline (mean)	159	163
Change from baseline (adjusted mean***)	-5	8
Difference from placebo (adjusted mean) (95% CI)	-13 (-18, -7)	--

SU=sulfonylurea

*Full analysis population using last observation on study

**Linagliptin 5 mg + Metformin + SU, n=742; Placebo + Metformin + SU, n=247

***HbA1c: ANCOVA model included treatment as class-effects and baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

14.5 Add-On Combination Therapy with Insulin

A total of 1261 patients with type 2 diabetes inadequately controlled on basal insulin alone or basal insulin in combination with oral drugs participated in a randomized, double-blind placebo-controlled trial designed to evaluate the efficacy of linagliptin as add-on therapy to basal insulin over 24 weeks. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), renal function impairment status (based on baseline eGFR), and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin + pioglitazone). Patients with a baseline A1C of ≥7% and ≤10% were included in the study including 709 patients with renal impairment (eGFR <90 mL/min), most of whom (n=575) were categorized as mild renal impairment (eGFR 60 to <90 mL/min). Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or pioglitazone background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of either 5 mg of linagliptin or placebo, administered once daily. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 24 weeks of treatment. Patients who failed to meet specific glycemic goals during the double-blind treatment period were rescued by increasing background insulin dose.

Linagliptin used in combination with insulin (with or without metformin and/or pioglitazone), provided statistically significant improvements in A1C and FPG compared to placebo (Table 10) after 24 weeks of treatment. The mean total daily insulin dose at baseline was 42 units for patients treated with linagliptin and 40 units for patients treated with placebo. Background baseline diabetes therapy included use of: insulin alone (16.1%), insulin combined with metformin only (75.5%), insulin combined with metformin and pioglitazone (7.4%), and insulin combined with pioglitazone only (1%). The mean change from baseline to Week 24 in the daily dose of insulin was +1.3 IU in the placebo group and +0.6 IU in the linagliptin group. The mean change in body weight from baseline to Week 24 was similar in the two treatment groups. The rate of hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self measured blood glucose was also similar in both groups (21.4% linagliptin; 22.9% placebo) in the first 24 weeks of the study.

Table 10 Glycemic Parameters in Placebo-Controlled Study for Linagliptin in Combination with Insulin*

	Linagliptin 5 mg + Insulin	Placebo + Insulin
A1C (%)		
Number of patients	n=618	n=617
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean***)	-0.6	0.1
Difference from placebo (adjusted mean) (95% CI)	-0.7 (-0.7, -0.6)	--
Patients [n (%)] achieving A1C <7%**	116 (19.5)	48 (8.1)
FPG (mg/dL)		
Number of patients	n=613	n=608
Baseline (mean)	147	151
Change from baseline (adjusted mean***)	-8	3
Difference from placebo (adjusted mean) (95% CI)	-11 (-16, -6)	--

*Full analysis population using last observation carried forward (LOCF) method on study

**Linagliptin + Insulin, n=595; Placebo + Insulin, n=593

***HbA1c: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

The difference between treatment with linagliptin and placebo in terms of adjusted mean change from baseline in HbA1c after 24 weeks was comparable for patients with no renal impairment (eGFR ≥90 mL/min, n=539), with mild renal impairment (eGFR 60 to <90 mL/min, n=565), or with moderate renal impairment (eGFR 30 to <60 mL/min, n=124).

14.6 Renal Impairment

A total of 133 patients with type 2 diabetes participated in a 52 week, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of linagliptin in patients with both type 2 diabetes and severe chronic renal impairment. Participants with an estimated (based on the four variables modified diet in renal disease [MDRD] equation) GFR value of <30 mL/min were eligible to participate in the study. Randomization was stratified by baseline HbA1c ($\leq 8\%$ and $>8\%$) and background antidiabetic therapy (insulin or any combination with insulin, SU or glinides as monotherapy and pioglitazone or any other antidiabetics excluding any other DPP-4 inhibitors). For the initial 12 weeks of the study, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dose adjustments in antidiabetic background therapy were allowed. At baseline in this trial, 62.5% of patients were receiving insulin alone as background diabetes therapy, and 12.5% were receiving sulfonylurea alone.

After 12 weeks of treatment, linagliptin 5 mg provided statistically significant improvement in A1C compared to placebo, with an adjusted mean change of -0.6% compared to placebo (95% confidence interval -0.9, -0.3) based on the analysis using last observation carried forward (LOCF). With adjustments in antidiabetic background therapy after the initial 12 weeks, efficacy was maintained for 52 weeks, with an adjusted mean change from baseline in A1C of -0.7% compared to placebo (95% confidence interval -1.0, -0.4) based on analysis using LOCF.

16 HOW SUPPLIED/STORAGE AND HANDLING

JENTADUETO (linagliptin and metformin hydrochloride) tablets 2.5 mg/500 mg are supplied as follows:

Bottles of 60 (NDC 0597-0146-60)

Bottles of 180 (NDC 0597-0146-18)

JENTADUETO (linagliptin and metformin hydrochloride) tablets 2.5 mg/850 mg are supplied as follows:

Bottles of 60 (NDC 0597-0147-60)

Bottles of 180 (NDC 0597-0147-18)

JENTADUETO (linagliptin and metformin hydrochloride) tablets 2.5 mg/1000 mg are supplied as follows:

Bottles of 60 (NDC 0597-0148-60)

Bottles of 180 (NDC 0597-0148-18)

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from exposure to high humidity. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Instructions

Inform patients of the potential risks and benefits of JENTADUETO and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Inform patients of the risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development [see *Warnings and Precautions* (5.1)]. Advise patients to discontinue JENTADUETO immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, slow or irregular heart beat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. GI symptoms are common during initiation of metformin treatment and may occur during initiation of JENTADUETO therapy; however, advise patients to consult their doctor if they develop unexplained symptoms. Although GI symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to metformin-induced lactic acidosis or other serious disease.

Inform patients that the risk of hypoglycemia is increased when JENTADUETO is used in combination with an insulin secretagogue (e.g., sulfonylurea), and that a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Inform patients that acute pancreatitis has been reported during postmarketing use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue JENTADUETO promptly and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions* (5.2)].

Instruct patients to take JENTADUETO only as prescribed. If a dose is missed, advise patients not to double their next dose.

Warn patients against excessive alcohol intake, either acute or chronic, while receiving JENTADUETO [see *Warnings and Precautions* (5.6)].

Inform patients about the importance of regular testing of renal function and hematological parameters when receiving treatment with JENTADUETO.

Instruct patients to read the Medication Guide before starting JENTADUETO therapy and to reread each time the prescription is renewed. Instruct patients to inform their doctor if they develop any bothersome or unusual symptom, or if any symptom persists or worsens.

17.2 Laboratory Tests

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels toward the normal range. A1C monitoring is especially useful for evaluating long-term glycemic control.

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B₁₂ deficiency should be excluded.

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MEDICATION GUIDE

JENTADUETO (JEN ta doo e' toe) (linagliptin and metformin hydrochloride) Tablets

Read this Medication Guide carefully before you start taking JENTADUETO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about JENTADUETO, ask your doctor or pharmacist.

What is the most important information I should know about JENTADUETO?

Serious side effects can happen in people taking JENTADUETO, including:

- 1. Lactic Acidosis.** Metformin, one of the medicines in JENTADUETO, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking JENTADUETO and call your doctor right away if you get any of the following symptoms of lactic acidosis:

- feel very weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have unusual sleepiness or sleep longer than usual
- have sudden stomach or intestinal problems with nausea and vomiting or diarrhea
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis if you:

- have kidney problems. People whose kidneys are not working properly should not take JENTADUETO.
 - have liver problems
 - have congestive heart failure that requires treatment with medicines
 - drink alcohol very often, or drink a lot of alcohol in short-term ("binge" drinking)
 - get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
 - have certain x-ray tests with dyes or contrast agents that are injected into your body
 - have surgery
 - have a heart attack, severe infection, or stroke
 - are 80 years of age or older and have not had your kidneys tested
- 2. Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking JENTADUETO:

Tell your doctor if you have ever had:

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

Stop taking JENTADUETO and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JENTADUETO?

- JENTADUETO is a prescription medicine that contains 2 diabetes medicines, linagliptin and metformin. JENTADUETO can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate.
- JENTADUETO is not for people with type 1 diabetes.
- JENTADUETO is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take JENTADUETO.
- It is not known if JENTADUETO is safe and effective in children under 18 years of age.

Who should not take JENTADUETO?

Do not take JENTADUETO if you:

- have kidney problems
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to linagliptin, metformin, or any of the ingredients in JENTADUETO. See the end of this Medication Guide for a complete list of ingredients in JENTADUETO.

Symptoms of a serious allergic reaction to JENTADUETO may include:

- skin rash, itching, flaking or peeling
- raised red patches on your skin (hives)
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- difficulty with swallowing or breathing

If you have any of these symptoms, stop taking JENTADUETO and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before using JENTADUETO?

Before you take JENTADUETO, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems

- have liver problems
- have heart problems, including congestive heart failure
- drink alcohol very often, or drink a lot of alcohol in short term "binge" drinking
- are 80 years of age or older, you should not take JENTADUETO unless your kidneys have been checked and they are normal
- are going to get an injection of dye or contrast agents for an x-ray procedure. JENTADUETO will need to be stopped for a short time. Talk to your doctor about when you should stop JENTADUETO and when you should start JENTADUETO again. See **"What is the most important information I should know about JENTADUETO?"**
- have type 1 diabetes. JENTADUETO should not be used to treat people with type 1 diabetes.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if JENTADUETO will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if JENTADUETO passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take JENTADUETO.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. JENTADUETO may affect the way other medicines work, and other medicines may affect how JENTADUETO works.

Especially tell your doctor if you take:

- other medicines that can lower your blood sugar
- rifampin* (Rifadin[®], Rimactane[®], Rifater[®], Rifamate[®]), an antibiotic that is used to treat tuberculosis

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take JENTADUETO?

- Take JENTADUETO exactly as your doctor tells you to take it.
- Take JENTADUETO 2 times each day with meals. Taking JENTADUETO with meals may lower your chance of having an upset stomach.
- If you miss a dose, take it with food as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of JENTADUETO at the same time.
- If you take too much JENTADUETO, call your doctor or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.
- Your doctor may tell you to take JENTADUETO along with other diabetes medicines. Low blood sugar can happen more often when JENTADUETO is taken with certain other diabetes medicines. See **"What are the possible side effects of JENTADUETO?"**

- You may need to stop taking JENTADUETO for a short time. Call your doctor for instructions if you:
 - are dehydrated (have lost too much body fluid). Dehydration can occur if you are sick with severe vomiting, diarrhea, or fever, or if you drink a lot less fluid than normal.
 - plan to have surgery
 - are going to get an injection of dye or contrast agent for an x-ray procedure. See "**What is the most important information I should know about JENTADUETO?**" and "**Who should not take JENTADUETO?**".
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JENTADUETO.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JENTADUETO.

What are the possible side effects of JENTADUETO tablets?

JENTADUETO may cause serious side effects, including:

- See "**What is the most important information I should know about JENTADUETO?**"
- **low blood sugar (hypoglycemia).** If you take JENTADUETO with another medication that can cause low blood sugar, such as sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JENTADUETO. Signs and symptoms of low blood sugar may include:

• headache	• irritability
• hunger	• drowsiness
• fast heart beat	• weakness
• sweating	• dizziness
• feeling jittery	• confusion

The most common side effects of JENTADUETO include:

- stuffy or runny nose and sore throat
- diarrhea

These are not all the possible side effects of JENTADUETO. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JENTADUETO tablets?

- Store JENTADUETO between 68°F and 77°F (20°C and 25°C).
- Keep tablets dry.

Keep JENTADUETO and all medicines out of the reach of children.**General information about the safe and effective use of JENTADUETO**

Medicines are sometimes prescribed for purposes other than those listed in Medication Guides. Do not use JENTADUETO for a condition for which it was not prescribed. Do not give JENTADUETO to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JENTADUETO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JENTADUETO that is written for health professionals.

For more information, go to www.jentadueto.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in JENTADUETO?

Active Ingredients: linagliptin and metformin hydrochloride

Inactive Ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc.

2.5 mg/500 mg and 2.5 mg/850 mg tablets also contain yellow ferric oxide.

2.5 mg/850 mg and 2.5 mg/1000 mg tablets also contain red ferric oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and/or the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar to a normal level. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

Talk to your doctor about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and other problems you have because of your diabetes.

This Medication Guide has been approved by the U. S. Food and Drug Administration.

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MEDICATION GUIDE
KAZANO (Kah-ZAHN-oh)
(alogliptin and metformin HCl)
tablets

Read this Medication Guide carefully before you start taking KAZANO and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about KAZANO, ask your doctor or pharmacist.

What is the most important information I should know about KAZANO?

KAZANO can cause serious side effects, including:

1. **Lactic Acidosis.** Metformin, one of the medicines in KAZANO, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking KAZANO and call your doctor right away if you get any of the following symptoms of lactic acidosis:

- feel very weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have unusual sleepiness or sleep longer than usual
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a slow or irregular heartbeat

You have a higher chance for getting lactic acidosis with KAZANO if you:

- have kidney problems. People whose kidneys are not working properly should not take KAZANO
 - have liver problems
 - have congestive heart failure that requires treatment with medicines
 - drink a lot of alcohol (very often or short-term “binge” drinking)
 - get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
 - have certain x-ray tests with injectable dyes or contrast agents
 - have surgery
 - have a heart attack, severe infection or stroke
2. **Inflammation of the pancreas (pancreatitis).** Alogliptin, one of the medicines in KAZANO, may cause pancreatitis, which may be severe.

Certain medical conditions make you more likely to get pancreatitis.

Before you start taking KAZANO:

Tell your doctor if you have ever had:

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- kidney problems
- liver problems

Stop taking KAZANO and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is KAZANO?

- KAZANO contains 2 prescription diabetes medicines, alogliptin (NESINA) and metformin hydrochloride.
- KAZANO is a prescription medicine used with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- KAZANO is not for people with type 1 diabetes.
- KAZANO is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if KAZANO is safe and effective in children under the age of 18.

Who should not take KAZANO?

Do not take KAZANO if you:

- have kidney problems
- have a condition called metabolic acidosis or have had diabetic ketoacidosis (increased ketones in your blood or urine)
- are going to get an injection of dye or contrast agents for an x-ray procedure, KAZANO will need to be stopped for a short time. Talk to your doctor about when you should stop KAZANO and when you should start KAZANO again
- are allergic to alogliptin (NESINA) or metformin or any of the ingredients in KAZANO or have had a serious allergic (hypersensitivity) reaction to alogliptin or metformin. See the end of this Medication Guide for a complete list of the ingredients in KAZANO

Symptoms of a serious allergic reaction to KAZANO may include:

- o swelling of your face, lips, throat and other areas on your skin
- o difficulty with swallowing or breathing
- o raised, red areas on your skin (hives)
- o skin rash, itching, flaking or peeling

If you have any of these symptoms, stop taking KAZANO and contact your doctor right away or go to the nearest hospital emergency room.

What should I tell my doctor before and during treatment with KAZANO?

Before you take KAZANO, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have kidney or liver problems
- have heart problems, including congestive heart failure
- are older than 80 years, you should not take KAZANO unless your kidneys have been checked and they are normal
- drink alcohol very often or drink a lot of alcohol in short-term “binge” drinking
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if KAZANO will harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known whether KAZANO passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking KAZANO

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start any new medicine.

KAZANO may affect the way other medicines work, and other medicines may affect how KAZANO works. Contact your doctor before you start or stop other types of medicines.

How should I take KAZANO?

- Take KAZANO exactly as your doctor tells you to take it.
- Take KAZANO 2 times each day.
- Take KAZANO with food to lower your chances of having an upset stomach.
- Do not break or cut KAZANO tablets before swallowing.
- Your doctor may need to change your dose of KAZANO to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose, and take the next dose at your regular schedule. Do not take 2 doses of KAZANO at the same time.
- If you take too much KAZANO, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start KAZANO and during treatment as needed. Your doctor may ask you to stop taking KAZANO based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of KAZANO?

KAZANO can cause serious side effects, including:

- See “**What is the most important information I should know about KAZANO?**”
- **Allergic (hypersensitivity) reactions**, such as:
 - o swelling of your face, lips, throat and other areas on your skin
 - o difficulty swallowing or breathing
 - o raised, red areas on your skin (hives)
 - o skin rash, itching, flaking or peeling
 If you have these symptoms, stop taking KAZANO and contact your doctor right away.
- **Liver problems.** Call your doctor right away if you have symptoms, such as:
 - o nausea or vomiting
 - o stomach pain
 - o unusual or unexplained tiredness
 - o loss of appetite
 - o dark urine
 - o yellowing of your skin or the whites of your eyes
- **Low blood sugar (hypoglycemia).** If you take KAZANO with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take KAZANO. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, and then call your doctor. Signs and symptoms of low blood sugar may include:

• shaking or feeling jittery	• headache
• sweating	• change in mood
• fast heartbeat	• confusion
• change in vision	• dizziness
• hunger	

The most common side effects of KAZANO include:

- cold-like symptoms (upper respiratory tract infection)
- stuffy or runny nose and sore throat
- diarrhea
- increase in blood pressure
- headache
- back pain
- urinary tract infection

Taking KAZANO with food can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unexplained stomach problems, tell your doctor. Stomach problems that start later, during treatment, may be a sign of something more serious.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KAZANO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KAZANO?

- Store KAZANO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of KAZANO tightly closed.

Keep KAZANO and all medicines out of the reach of children.

General information about the safe and effective use of KAZANO

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take KAZANO for a condition for which it was not prescribed. Do not give KAZANO to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about KAZANO. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about KAZANO that is written for health professionals.

For more information go to www.kazano.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in KAZANO?

Active ingredients: alogliptin and metformin hydrochloride

Inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone and magnesium stearate; the tablets are film-coated with hypromellose 2910, talc, titanium dioxide and ferric oxide yellow.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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ALM143P R3

The following information is intended to supplement, not substitute for, the expertise and judgment of your physician, pharmacist or other healthcare professional. It should not be construed to indicate that the use of the drug is safe, appropriate, or effective for you. Consult your healthcare professional before taking this drug.

Pioglitazone Tablets

Generic Name: pioglitazone hydrochloride

Dosage Form: tablet

BOXED WARNING

- Thiazolidinediones, including pioglitazone hydrochloride, cause or exacerbate congestive heart failure in some patients [see Warnings and Precautions(5.1)].
- After initiation of pioglitazone hydrochloride, and after dose increases, monitor patients carefully for signs and symptoms of heart failure(e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone tablets must be considered.
- Pioglitazone hydrochloride is not recommended in patients with symptomatic heart failure.
- Initiation of Pioglitazone Tablets in patients with established New York Heart Association(NYHA)Class III or IV heart failure is contraindicated [see Contraindications(4)and Warnings and Precautions(5.1)].

INDICATIONS & USAGE

Monotherapy and Combination Therapy

Pioglitazone Tablets USP are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings [see Clinical Studies (14)].

Important Limitation of Use

Pioglitazone Tablets USP exerts its antihyperglycemic effect only in the presence of endogenous insulin. Pioglitazone Tablets USP should not be used to treat type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

Use caution in patients with liver disease [see Warnings and Precautions (5.3)].

DOSAGE & ADMINISTRATION

Recommendations for all patients

Pioglitazone tablets should be taken once daily and can be taken without regard to meals. The recommended starting dose for patients without congestive heart failure is 15 mg or 30 mg once daily.

The recommended starting dose for patients with congestive heart failure (NYHA Class I or II) is 15 mg once daily. The dose can be titrated in increments of 15 mg up to a maximum of 45 mg once daily based on glycemic response as determined by HbA1c.

After initiation of pioglitazone hydrochloride or with dose increase, monitor patients carefully for adverse reactions related to fluid retention such as weight gain, edema, and signs and symptoms of congestive heart failure [see Boxed Warning and Warnings and Precautions (5.2)].

Liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) should be obtained prior to initiating Pioglitazone Tablets. Routine periodic monitoring of liver tests during treatment with Pioglitazone Tablets is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of pioglitazone hydrochloride or who are found to have abnormal liver tests while taking Pioglitazone Tablets should be managed as described under Warnings and Precautions [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Concomitant use with an insulin secretagogue or insulin

If hypoglycemia occurs in a patient co-administered pioglitazone hydrochloride and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced.

If hypoglycemia occurs in a patient co-administered pioglitazone hydrochloride and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response

Coadministration with strong CYP2C8 inhibitors

Coadministration of pioglitazone hydrochloride and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of pioglitazone tablet is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

DOSAGE FORMS & STRENGTHS

Round tablet contains pioglitazone as follows:

- 15 mg: White to off white, circular, flat face, bevelled edge, uncoated tablet debossed with “ML 86” on one side and plain on the other side
- 30 mg: White to off white, circular, flat face, bevelled edge, uncoated tablet debossed with “ML 87” on one side and plain on the other side
- 45 mg: White to off white, circular, flat face, bevelled edge, uncoated tablet debossed with “ML 91” on one side and plain on the other side

Contraindications

Do not initiate in patients with NYHA Class III or IV heart failure [see Boxed Warning]. Do not use in patients with a history of a serious hypersensitivity reaction to Pioglitazone Tablets or any of its ingredients.

Warnings and Precautions

Congestive Heart Failure

Pioglitazone hydrochloride, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone hydrochloride is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of Pioglitazone Tablets must be considered [see Boxed Warning, Contraindications (4), and Adverse Reactions (6.1)].

Edema

In controlled clinical trials, edema was reported more frequently in patients treated with Pioglitazone Tablets than in placebo-treated patients and is dose-related [see Adverse Reactions (6.1)]. In postmarketing experience, reports of new onset or worsening edema have been received.

Pioglitazone hydrochloride should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone hydrochloride, can cause fluid retention, which can exacerbate or lead to congestive heart failure, pioglitazone hydrochloride should be used with caution in patients at risk for congestive heart failure. Patients treated with Pioglitazone Tablets should be monitored for signs and symptoms of congestive heart failure [see Boxed Warning, Warnings and Precautions (5.1) and Patient Counseling Information (17.1)].

Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking pioglitazone tablets, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone hydrochloride controlled clinical trial database to date [see Adverse Reactions (6.1)].

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating Pioglitazone Tablets therapy. In patients with abnormal liver tests, pioglitazone hydrochloride should be initiated with caution.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than 3 times the upper limit of the reference range), pioglitazone hydrochloride treatment should be interrupted and investigation done to establish the probable cause. Pioglitazone Tablets should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury, and should not be restarted on Pioglitazone Tablets. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with Pioglitazone Tablets can be used with caution.

Fractures

In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to Pioglitazone Tablets (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for Pioglitazone Tablets versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with Pioglitazone Tablets (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with Pioglitazone

Tablets and attention should be given to assessing and maintaining bone health according to current standards of care.

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see Nonclinical Toxicology (13.1)]. In two 3-year trials in which pioglitazone hydrochloride was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone hydrochloride compared to 5/3679 (0.14%) in patients not taking pioglitazone hydrochloride. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone hydrochloride and two (0.05%) cases on placebo.

A five-year interim report of an ongoing 10-year observational cohort study found a non-significant increase in the risk for bladder cancer in subjects ever exposed to pioglitazone hydrochloride, compared to subjects never exposed to pioglitazone hydrochloride (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of pioglitazone hydrochloride therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of pioglitazone hydrochloride use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking pioglitazone hydrochloride longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without pioglitazone hydrochloride] to approximately 10 in 10,000 [with pioglitazone hydrochloride]).

There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, pioglitazone hydrochloride should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone hydrochloride should be considered in patients with a prior history of bladder cancer.

Hypoglycemia

Patients receiving pioglitazone hydrochloride in combination with insulin or other anti-diabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant anti-diabetic medication may be necessary to reduce the risk of hypoglycemia [see Dosage and Administration (2.2)].

Macular Edema

Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone hydrochloride or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of the thiazolidinedione.

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings [see Adverse Reactions (6.1)].

Ovulation

Therapy with pioglitazone hydrochloride, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking Pioglitazone Tablets [see Use in Specific Populations (8.1)]. This effect has not been investigated in clinical trials, so the frequency of this occurrence is not known. Adequate contraception in all premenopausal women treated with pioglitazone tablet is recommended.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone hydrochloride or any other anti-diabetic drug.

Adverse Reactions

The following serious adverse reactions are discussed elsewhere in the labeling:

- Congestive heart failure [see Boxed Warning and Warnings and Precautions (5.1)]
- Edema [see Warnings and Precautions (5.2)]
- Fractures [see Warnings and Precautions (5.4)]

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

MEDICATION GUIDE
OSENI (OH-senn-ee)
(alogliptin and pioglitazone)
tablets

Read this Medication Guide carefully before you start taking OSENI and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about OSENI, ask your doctor or pharmacist.

What is the most important information I should know about OSENI?

OSENI can cause serious side effects, including:

- 1. New or worse heart failure:** Pioglitazone, one of the medicines in OSENI, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
 - Do not take OSENI if you have severe heart failure.
 - If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, OSENI may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
 - shortness of breath or trouble breathing, especially when you lie down
 - an unusually fast increase in weight
 - unusual tiredness
- 2. Inflammation of the pancreas (pancreatitis):** Alogliptin, one of the medicines in OSENI, may cause pancreatitis, which may be severe.

Certain medical conditions make you more likely to get pancreatitis.

Before you start taking OSENI:

Tell your doctor if you have ever had:

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- kidney problems
- liver problems

Stop taking OSENI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is OSENI?

- OSENI contains 2 prescription diabetes medicines, alogliptin (NESINA) and pioglitazone (ACTOS).
- OSENI is a prescription medicine used with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- OSENI is not for people with type 1 diabetes.
- OSENI is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if OSENI is safe and effective in children under the age of 18. OSENI is not recommended for use in children.

Who should not take OSENI?

Do not take OSENI if you:

- have severe heart failure
- are allergic to alogliptin (NESINA), pioglitazone (ACTOS) or any ingredient in OSENI or have had a serious allergic (hypersensitivity) reaction to alogliptin or pioglitazone. See the end of this Medication Guide for a complete list of the ingredients in OSENI.

Symptoms of a serious allergic reaction to OSENI may include:

- o swelling of your face, lips, throat and other areas on your skin
- o difficulty with swallowing or breathing
- o raised, red areas on your skin (hives)
- o skin rash, itching, flaking or peeling

If you have these symptoms, stop taking OSENI and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with OSENI?

Before you start taking OSENI, tell your doctor if you:

- have heart failure
- have a type of diabetic eye disease that causes swelling of the back of the eye (macular edema)
- have kidney or liver problems
- have or have had inflammation of the pancreas (pancreatitis)
- have or have had cancer of the bladder
- have other medical conditions
- **are pregnant or plan to become pregnant.** It is not known if OSENI can harm your unborn baby. Talk to your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant.
- **are a premenopausal woman who does not have periods regularly or at all.** OSENI may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking OSENI. Tell your doctor right away if you become pregnant while taking OSENI.

- **are breastfeeding or plan to breastfeed.** It is not known whether OSENI passes into your breast milk and if it can harm your baby. You should not take OSENI if you breastfeed your baby. Talk with your doctor about the best way to feed your baby if you are taking OSENI.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start a new medicine.

OSENI may affect the way other medicines work, and other medicines may affect how OSENI works. Contact your doctor before you start or stop other types of medicines.

How should I take OSENI?

- Take OSENI exactly as your doctor tells you to take it.
- Take OSENI 1 time each day with or without food.
- Do not break or cut OSENI tablets before swallowing.
- Your doctor may need to change your dose of OSENI to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and take the next dose at your regular time. **Do not** take 2 doses of OSENI at the same time.
- If you take too much OSENI, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start OSENI and during treatment as needed. Your doctor may change your dose of OSENI based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor should check your eyes regularly while you take OSENI.

What are the possible side effects of OSENI?

OSENI can cause serious side effects, including:

- See “**What is the most important information I should know about OSENI?**”
- **Allergic (hypersensitivity) reactions**, such as:
 - o swelling of your face, lips, throat and other areas on your skin
 - o difficulty with swallowing or breathing
 - o raised, red areas on your skin (hives)
 - o skin rash, itching, flaking or peeling

If you have these symptoms, stop taking OSENI and contact your doctor right away.

- **Liver problems.** Call your doctor right away if you have unexplained symptoms such as:
 - o nausea or vomiting
 - o stomach pain
 - o unusual or unexplained tiredness
 - o loss of appetite
 - o dark urine
 - o yellowing of your skin or the whites of your eyes
- **Broken bones (fractures).** Usually in the hand, upper arm or foot in women. Talk to your doctor for advice on how to keep your bones healthy.
- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take OSENI. You should not take OSENI if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
 - o blood or a red color in your urine
 - o an increased need to urinate
 - o pain while you urinate
- **Low blood sugar (hypoglycemia).** If you take OSENI with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take OSENI. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Signs and symptoms of low blood sugar may include:

o shaking or feeling jittery	o headache
o sweating	o change in mood
o fast heartbeat	o confusion
o change in vision	o dizziness
o hunger	
- **Diabetic eye disease with swelling in the back of the eye (macular edema).** Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly.
- **Release of an egg from an ovary in a woman (ovulation) leading to pregnancy.** Ovulation may happen when premenopausal women who do not have regular monthly periods take OSENI. This can increase your chance of getting pregnant.

The most common side effects of OSENI include:

- stuffy or runny nose and sore throat
- back pain
- cold-like symptoms (upper respiratory tract infection)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OSENI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OSENI?

- Store OSENI at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep container tightly closed and protect from moisture and humidity.

Keep OSENI and all medicines out of the reach of children.

General information about the safe and effective use of OSENI

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take OSENI for a condition for which it was not prescribed. Do not give OSENI to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about OSENI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about OSENI that is written for health professionals.

For more information, go to www.oseni.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in OSENI?

Active ingredients: alogliptin and pioglitazone.

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate; the tablets are film-coated with hypromellose, polyethylene glycol, titanium dioxide, talc and ferric oxide (yellow and/or red) and are marked with red A1 or gray F1 printing ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:

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Deerfield, IL 60015

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ALP008 R3

Article Link: <http://diabetes.webmd.com/sulfonylureas-for-type-2-diabetes>

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- [Gestational Diabetes](#)
- [Health Check: Type 2 Diabetes](#)
- [Prediabetes](#)
- [Insulin Pump](#)

Diabetes Health Center

Sulfonylureas for Type 2 Diabetes

Examples

Generic Name	Brand Name
chlorpropamide	Diabinese
glimepiride	Amaryl
glipizide	Glucotrol, Glucotrol XL
glyburide	DiaBeta, Glynase PresTab, Micronase
tolazamide	
tolbutamide	

Sulfonylureas are also available in combination pills. Glyburide is combined with the [biguanide](#) medicine [metformin](#) ([Glucovance](#)). [Glipizide](#) is combined with metformin ([Metaglip](#)). [Glimepiride](#) is combined with the [thiazolidinedione](#) medicines [rosiglitazone](#) ([Avandaryl](#)) and [pioglitazone](#) ([Duetact](#)).

How It Works

Sulfonylurea medicines increase the amount of [insulin](#) produced by the [pancreas](#), and [insulin](#) lowers [blood](#) sugar.

Why It Is Used

Sulfonylurea medicines are prescribed for people with [type 2 diabetes](#) when eating healthy foods, [weight loss](#), and [exercise](#) do not keep the blood sugar level within a [target range](#). They are helpful for people who cannot make enough insulin or who have become resistant to the insulin the body makes.

These medicines can help control [blood sugar levels](#) in children and young adults who have [type 2 diabetes](#) and are [overweight](#).

How Well It Works

Type 2 diabetes is a disease that can get worse over time, so medicines may need to change.

Diabetes medicines work best for people who are being active and eating healthy foods. Studies have suggested that sulfonylureas lower [hemoglobin A1c](#) by 1% to 2%.¹

Side Effects

All medicines have side effects. But many people don't feel the side effects, or they are able to deal with them. Ask your pharmacist about the side effects of each medicine you take. Side effects are also listed in the information that comes with your medicine.

Here are some important things to think about:

- Usually the benefits of the medicine are more important than any minor side effects.
- Side effects may go away after you take the medicine for a while.
- If side effects still bother you and you wonder if you should keep taking the medicine, **call your doctor**. He or she may be able to lower your dose or change your medicine. Do not suddenly quit taking your medicine unless your doctor tells you to.

Call 911 or other emergency services right away if you have:

- [Trouble breathing](#).
- [Hives](#).
- Swelling of your face, lips, [tongue](#), or throat.

Call your doctor if you have:

- [Seizures](#).

Common side effects of this medicine include:

- Signs of [low blood sugar](#) ([sweating](#), feeling nervous, [dizziness](#), and/or confusion).
- [Hunger](#).
- [Weight gain](#).

See Drug Reference for a full list of side effects. (Drug Reference is not available in all systems.)

What To Think About

Sulfonylurea medicines increase insulin levels even if you have not eaten food. Watch for symptoms of low blood sugar, especially if you drink alcohol.

People with kidney or liver problems might not be able to take sulfonylurea medicines.

Skin can be more easily sunburned when taking tolbutamide or tolazamide. Chlorpropamide can cause a skin rash.

Taking medicine

Medicine is one of the many tools your doctor has to treat a health problem. Taking medicine as your doctor suggests will improve your health and may prevent future problems. If you don't take your medicines properly, you may be putting your health (and perhaps your life) at risk.

There are many reasons why people have trouble taking their medicine. But in most cases, there is something you can do. For suggestions on how to work around common problems, see the topic [Taking Medicines as Prescribed](#).

Advice for women

If you are [pregnant](#), [breast-feeding](#), or planning to get pregnant, do not use any medicines unless your doctor tells you to. Some medicines can harm your baby. This includes prescription and over-the-counter medicines, vitamins, herbs, and [supplements](#). And make sure that all your doctors know that you are pregnant, breast-feeding, or planning to get pregnant.

Checkups

Follow-up care is a key part of your treatment and safety. Be sure to make and go to all appointments, and call your doctor if you are having problems. It's also a good idea to know your test results and keep a list of the medicines you take.

Sulfonylurea medicines are an effective treatment for many people who have type 2 diabetes. If one of these medicines keeps your blood sugar within a target range, your risks of long-term complications of diabetes can be reduced. Other important factors that contribute to complications include [high blood pressure](#), being overweight, [high cholesterol](#) levels, and [smoking](#).

Complete the [new medication information form \(PDF\)](#) to help you understand this [medication](#).

Citations

- 1.American Diabetes Association (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. [Diabetes Care](#), 32: 193-203.

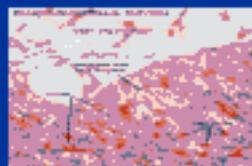
Top Picks

- [How Diabetic Retinopathy Affects Your Vision](#)
- [Images of Diabetic Retinopathy and Other Vision Problems](#)
- [Free Tool: Track Daily Sugar and Carb Intake](#)
- [Graze to Limit Blood Sugar Spikes](#)
- [Diabetes Warning Signs and Risk Factors](#)
- [4 Steps to a Healthier Diet](#)

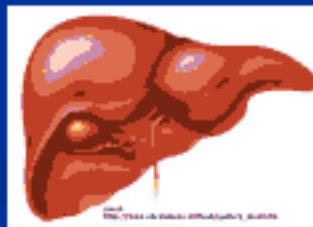
Proposed mechanism of action of Bromocriptine in relation to type 2 DM

- Diabetes patients may have low morning levels of hypothalamic dopamine, which is thought to lead to hyperglycemia and dyslipidemia
- CYCLOSET (special form of bromocriptine) is thought to reset aberrant low morning hypothalamic dopaminergic activity, which may reset neuroendocrine metabolic control

Decreased lipolysis in adipose tissue



Decreased postprandial hepatic glucose output



Decreased insulin resistance



Media Fact Sheet:

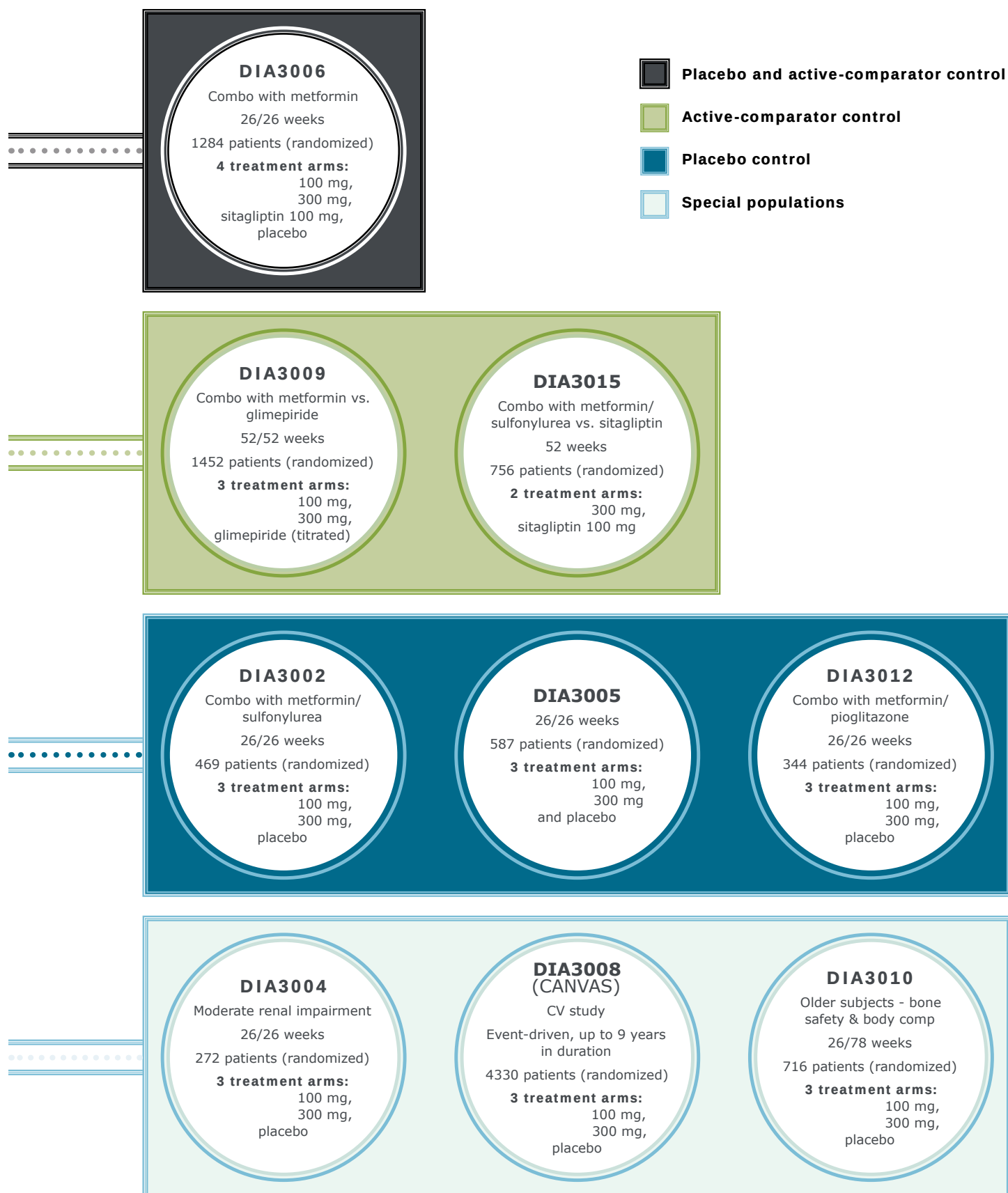
Phase 3 Program

Understanding the Phase 3 Program

FAST FACTS

- The global Phase 3 program evaluated the safety and efficacy of investigational antihyperglycemic agent canagliflozin, a selective sodium glucose co-transporter 2 (SGLT2) inhibitor, and enrolled 10,285 patients in nine studies.
- The trials assessed the safety and efficacy of canagliflozin dosed at 100 or 300 mg once daily, when used as monotherapy and in combination with oral antihyperglycemic agents, and in combination with insulin with or without oral antihyperglycemic agents.
- All clinical trials were global, randomized and double-blind, and were either placebo- or active comparator-controlled.
- The Phase 3 clinical program evaluated the safety and efficacy of investigational canagliflozin across the spectrum of type 2 diabetes management, from adult patients treated only with diet and exercise to those requiring insulin injections to maintain glycemic control, and in three large studies in special populations: older patients with type 2 diabetes, patients with type 2 diabetes who had moderate renal impairment, and patients with type 2 diabetes who had or were at high risk for cardiovascular disease.
- CANTATA (CANagliflozin n Treatment And Trial Analysis) includes multiple studies assessing the glucose-lowering efficacy and safety of canagliflozin in adult patients diagnosed with type 2 diabetes failing to achieve glycemic control on diet and exercise and on the background of a variety of commonly used oral antihyperglycemic agents or insulin.
- CANVAS (CANagliflozin cardioVascular Assessment Study) assesses the general safety, tolerability and cardiovascular safety of canagliflozin in approximately 4,330 adult patients with type 2 diabetes, who also have either a history or high risk of cardiovascular disease.

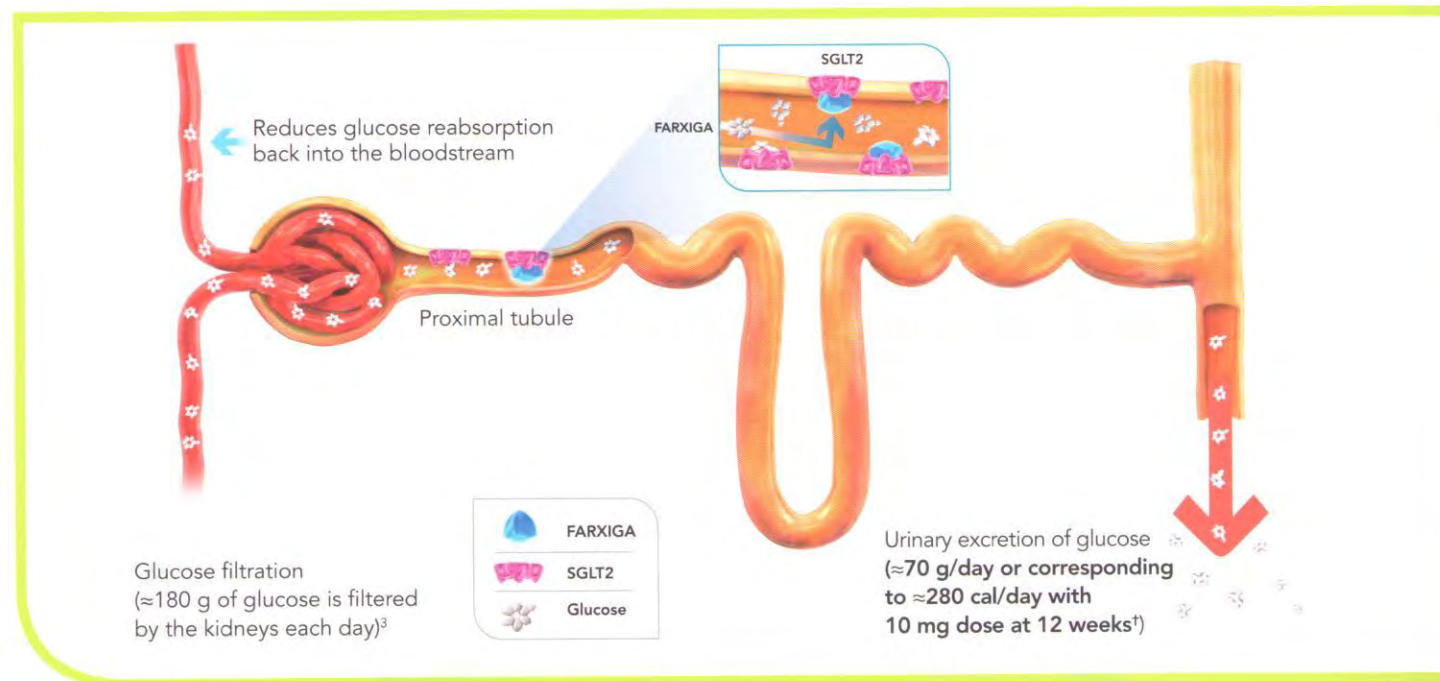
Phase 3 Clinical Development Program: 9 Studies Conducted



REMOVES GLUCOSE VIA RENAL EXCRETION

By inhibiting sodium-glucose cotransporter 2 (SGLT2), FARXIGA™ (dapagliflozin), a glucuretic, removes glucose and associated calories^{1,2}

- SGLT2 plays a primary role in removing glucose from the kidney filtrate and transports it back into the bloodstream



APPROXIMATELY

280

CALORIES

REMOVED PER DAY
AT 12 WEEKS¹

Improving Outcomes with SGLT2 Cotransporter Inhibitors in Challenging T2DM Patients

Frequently Asked Questions

How do SGLT2 inhibitors work to improve glycemic control in patients with type 2 diabetes mellitus (T2DM)?

SGLT2 inhibitors hinder glucose reabsorption in the proximal renal tubules, lowering blood glucose independent of insulin.

What is the effect of the SGLT2 inhibitor class on blood pressure?

SGLT2 inhibitors have been shown to lower systolic and diastolic blood pressure. These reductions may be a result of diuresis and body weight changes associated with SGLT2 inhibitors.

What is the recommended dosing for the two FDA-approved SGLT2 inhibitors?

Canagliflozin is initially dosed at 100 mg once daily and can be increased to 300 mg once daily in patients who require additional glycemic control. For dapagliflozin, the recommended starting dose is 5 mg once daily, taken in the morning, with or without food. This dose can be increased to 10 mg once daily for patients who require additional glycemic control.

What is the average reduction in A1C seen in patients on an SGLT2 inhibitor?

When used in monotherapy, SGLT2 inhibitors can reduce A1C from 0.5% to 0.9%, with the response usually dependent on baseline A1C.

What are the effects of SGLT2 therapy in patients taking insulin?

When added to insulin therapy, SGLT2 inhibitors have reduced A1C and weight.

What effects on weight have been seen with the SGLT2 inhibitors?

Glycosuria resulting from SGLT2 therapy is associated with a net caloric loss of approximately 200 to 300 kcal daily with statistically significant weight loss, when compared with placebo.

What effects on lipids have been reported with SGLT2 inhibitors?

Dose-related increases in LDL-C can occur with canagliflozin and dapagliflozin, and small increases in non-HDL-C can also occur with canagliflozin. Increases in HDL-C have also been noted with both agents. The cardiovascular significance of these changes is currently unknown and being assessed in long-term trials.

Have SGLT2 inhibitors been evaluated in patients 65 years and older?

In this patient population, a higher incidence of adverse effects related to reduced intravascular volume and smaller reductions in A1C have been reported, compared with younger individuals.

Should SGLT2 inhibitors be used in patients with moderate renal impairment?

Canagliflozin is not recommended for estimated glomerular filtration rates (eGFR) <45 mL/min/1.73m² and is contraindicated for eGFR <30 mL/min/1.73m², while dosage should not be increased above 100 mg daily if eGFR is between 45 and 60 mL/min/1.73m². Dapagliflozin is not recommended if eGFR is <60 mL/min/1.73m².

What are the effects on genital mycotic infections in patients taking SGLT2 inhibitors?

Dose-related increases in genital mycotic infections have been reported in both men and women taking SGLT2 inhibitors. In men, these infections are associated with balanitis or balanoposthitis.

What effects on serum potassium have been reported in patients taking SGLT2 inhibitors?

Dose-related, transient mean increases in serum potassium have been reported early after initiation of therapy, usually in patients with elevated potassium or renal impairment at baseline, or in patients using potassium-sparing diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

How should SGLT2 inhibitors be used for patients with T2DM?

SGLT2 inhibitors can be used as initial monotherapy and in combination with oral agents and/or insulin in patients with T2DM as an adjunct to diet and exercise to improve glycemic control. These medications are contraindicated in patients with severe renal impairment or end-stage renal disease and patients on dialysis.

References:

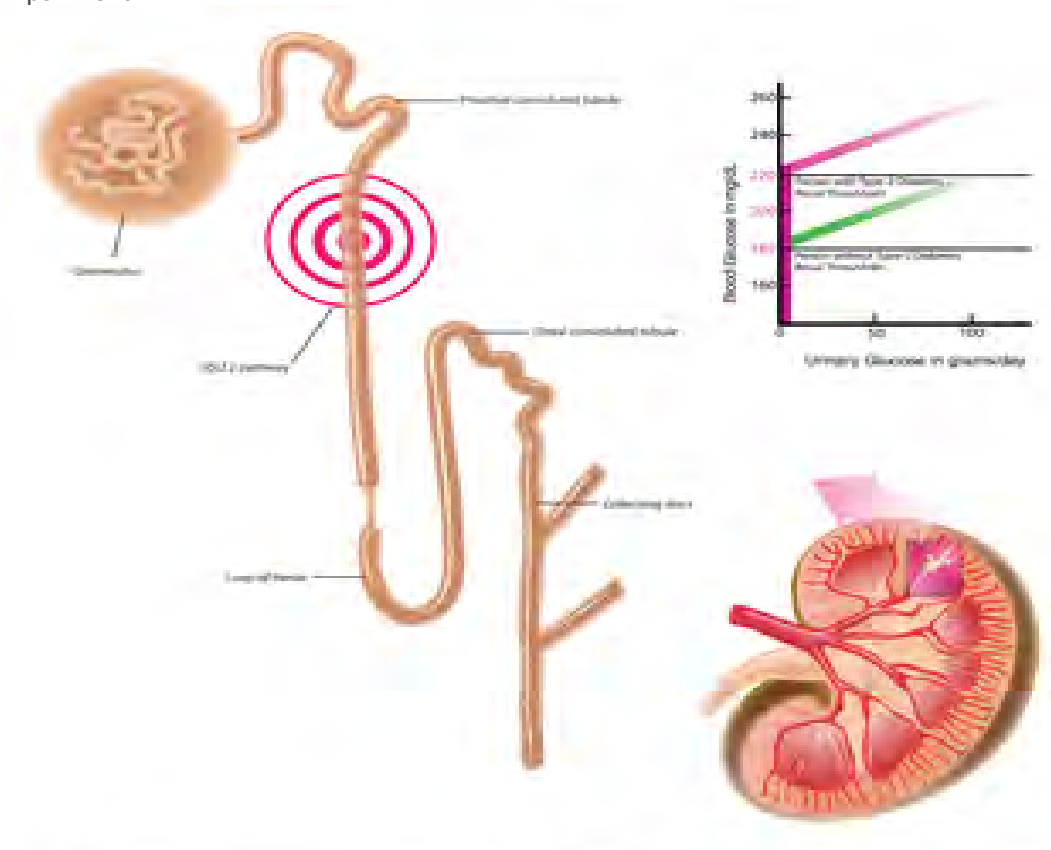
Canagliflozin [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.
Dapagliflozin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2014.

INVOKANA

cannagliflozin

Canagliflozin is a sodium glucose co-transporter 2, (SGLT2) inhibitor for the treatment of patients with type 2 diabetes. The kidneys of people with type 2 diabetes reabsorb greater amounts of glucose back into the body compared to non-diabetic people, which may contribute to elevated glucose levels. Canagliflozin blocks the reabsorption of glucose by the kidney, increasing glucose excretion and lowering blood glucose levels.

Type 2 diabetes is a chronic condition that over time may require the use of combinations of antihyperglycemic agents, including insulin, to maintain optimal glycemic control which is a primary goal of treatment. Canagliflozin has the potential to be administered as monotherapy in patients who are inadequately controlled with diet and exercise alone, as an add-on therapy in patients being treated with metformin alone or in combination with sulfonylureas, and in patients with moderate renal impairment.



The kidneys of people with type 2 diabetes reabsorb greater amounts of glucose back into the body compared to non-diabetic people, which may contribute to elevated glucose levels. Canagliflozin, an investigational SGLT2 inhibitor, blocks the reabsorption of glucose by the kidney, increasing glucose excretion and lowering blood glucose levels.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m²), end stage renal disease, or patients on dialysis.

WARNINGS and PRECAUTIONS

- Hypotension: INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m²), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- Impairment in Renal Function: INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².
- Hyperkalemia: INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
- Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- Genital Mycotic Infections: INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- Hypersensitivity Reactions: Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

- UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the

dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

- Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- Pregnancy Category C: Not for use in pregnancy, nursing mothers or in pediatric patients.
- Renal Impairment: The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to < 50 mL/min/1.73 m²). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥ 60 mL/min/1.73 m²); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

- Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

- There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session.

Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

- The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

K02CAN13149

[News](#) / FDA Approves SGLT2 Inhibitor STEGLATRO™ (ertugliflozin) and Fixed-Dose Combination STEGLUJAN™ (ertugliflozin and sitagliptin) for Adults with Type 2 Diabetes

FDA Approves SGLT2 Inhibitor STEGLATRO™ (ertugliflozin) and Fixed-Dose Combination STEGLUJAN™ (ertugliflozin and sitagliptin) for Adults with Type 2 Diabetes

Friday, December 22, 2017 - 7:00am
EST

Merck (NYSE:MRK), known as MSD outside the United States and Canada, and Pfizer Inc. (NYSE:PFE), today announced that the U.S. Food and Drug Administration (FDA) has approved STEGLATRO™ (ertugliflozin) tablets, an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor, and the fixed-dose combination STEGLUJAN™ (ertugliflozin and sitagliptin) tablets.

STEGLATRO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. STEGLUJAN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. STEGLATRO and STEGLUJAN are not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. STEGLUJAN has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using STEGLUJAN. STEGLATRO and STEGLUJAN are contraindicated in patients with severe renal impairment, end-stage renal disease or on dialysis, or with a history of a serious hypersensitivity reaction to ertugliflozin. STEGLUJAN is also contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin (such as anaphylaxis or angioedema). Additional safety information can be found below.

These FDA approvals are supported by seven Phase 3 studies of approximately 4,800 patients. STEGLATRO was studied as monotherapy and in combination with metformin and/or sitagliptin, as well as with insulin and a sulfonylurea, in adults with type 2 diabetes and moderate renal impairment. “In clinical trials, treatment with STEGLATRO resulted in significant A1C reductions when used alone or in combination with sitagliptin,” said Juan Pablo Frias, M.D., president and principal investigator, National Research Institute, Los Angeles. “This is important, as A1C-lowering is a key component of diabetes management, and many of my adult patients may need multiple medications to help manage their condition.”

“Merck welcomes the opportunity to provide adult patients with type 2 diabetes and their physicians these new medicines to help lower A1C, building on over a decade of experience with

our diabetes portfolio and reflecting our continued commitment to diabetes research and patient care,” said Keith Kaufman, M.D., vice president, global clinical development and therapeutic area head for diabetes, endocrinology and women’s health, Merck Research Laboratories.

Diabetes is a chronic, progressive disease affecting approximately 30 million Americans (90 to 95 percent have type 2 diabetes). About one-third of adults with type 2 diabetes in the U.S. are not at their A1C goal.

“There remains a need to help adults with type 2 diabetes improve their glycemic control, and as the prevalence of the disease continues to rise, we are pleased to offer additional treatment options to these patients and the healthcare providers who treat them,” said James Rusnak, M.D., Ph.D., senior vice president and chief development officer, internal medicine, Pfizer Global Product Development.

One of the studies supporting the FDA approvals was VERTIS SITA2, a 26-week double-blind, placebo-controlled study. VERTIS SITA2 evaluated STEGLATRO (ertugliflozin) compared to placebo in 463 patients with type 2 diabetes inadequately controlled (baseline A1C of 7.0-10.5%) on background metformin ($\geq 1,500$ mg/day) and sitagliptin (100 mg/day). Patients were randomized to STEGLATRO 5 mg, STEGLATRO 15 mg or placebo administered once daily, in addition to continuation of background metformin and sitagliptin therapy. In the study, STEGLATRO provided significant additional A1C reductions on top of metformin plus sitagliptin of 0.7 percent and 0.8 percent, respectively, for the 5 and 15 mg doses, compared with 0.2 percent for placebo ($p < 0.001$, for both comparisons), which was the study’s primary endpoint.

In this study, STEGLATRO significantly reduced body weight by 6.6 pounds with the 5 mg dose and 6.2 pounds with the 15 mg dose, on top of metformin plus sitagliptin, compared with 2.2 pounds with placebo. Baseline body weight was 193.1 pounds, 190.9 pounds and 190.6 pounds for the 5 mg, 15 mg and placebo groups, respectively. The difference from placebo was -4.2 pounds for STEGLATRO 5 mg (95% CI: -5.7, -2.9) and -4.0 pounds for STEGLATRO 15 mg (95% CI: -5.3, -2.6). STEGLATRO 5 mg and 15 mg were also associated with significant reductions in fasting plasma glucose (25.7 mg/dL and 32.1 mg/dL, respectively, vs. 6.5 mg/dL for placebo; $p < 0.001$, for both comparisons). Baseline fasting plasma glucose levels were 167.7 mg/dL, 171.7 mg/dL and 169.6 mg/dL for the 5 mg, 15 mg and placebo groups, respectively. Significant reductions in systolic blood pressure were also observed for STEGLATRO (3.8 mmHg for 5 mg and 4.5 mmHg for 15 mg, vs. 0.2 mmHg for placebo). Baseline systolic blood pressure values were 132.1 mmHg, 131.6 mmHg and 130.2 mmHg for the 5 mg, 15 mg and placebo groups, respectively. For systolic blood pressure, the difference from placebo was -3.7 mmHg for STEGLATRO (ertugliflozin) 5 mg (95% CI: -6.1, -1.2) and -4.3 mmHg for STEGLATRO 15 mg (95% CI: -6.7, -1.9). STEGLATRO is not indicated for weight loss or hypertension.

STEGLATRO causes intravascular volume contraction. Symptomatic hypotension may occur after initiating STEGLATRO, particularly in patients with impaired renal function (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m²), elderly patients (≥ 65 years), patients with low systolic blood pressure or patients on diuretics. Before initiating

STEGLATRO, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms after initiating therapy. Additional safety information can be found below.

In addition to STEGLATRO and STEGLUJAN (ertugliflozin and sitagliptin), the only fixed-dose combination of an SGLT2 inhibitor and the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin, the FDA also approved the fixed-dose combination SEGLUROMET™ (ertugliflozin and metformin hydrochloride). SEGLUROMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin. SEGLUROMET is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. The labeling for SEGLUROMET contains a boxed warning for lactic acidosis. SEGLUROMET is contraindicated in patients with severe renal impairment, end-stage renal disease or on dialysis, acute or chronic metabolic acidosis, including diabetic ketoacidosis, or a history of a serious hypersensitivity reaction to SEGLUROMET, ertugliflozin or metformin hydrochloride. Additional safety information is found below.

STEGLATRO is available in 5 mg and 15 mg tablets. STEGLUJAN combines 5 mg or 15 mg of ertugliflozin with 100 mg of sitagliptin. SEGLUROMET combines 2.5 mg or 7.5 mg of ertugliflozin with 500 mg or 1,000 mg of metformin hydrochloride.

Merck-Pfizer Collaboration and Product Availability

In 2013, Merck and Pfizer announced that they entered into a worldwide collaboration, except Japan, for the co-development and co-promotion of ertugliflozin. The Merck sales force will exclusively promote STEGLATRO and the two fixed-dose combination products in the United States. Merck and Pfizer will share potential revenues and certain costs on a 60/40 percent basis, respectively, and Pfizer may be entitled to additional milestone payments.

Merck has established a list price (Wholesale Acquisition Cost) of \$8.94 per day for STEGLATRO, \$17.45 per day for STEGLUJAN and \$8.94 per day for SEGLUROMET. Wholesale acquisition costs do not include discounts that may be paid on the products. STEGLATRO (ertugliflozin) and STEGLUJAN (ertugliflozin and sitagliptin) are expected to be available in pharmacies in January 2018. SEGLUROMET (ertugliflozin and metformin hydrochloride) is expected to be available in February 2018.

Selected Important Risk Information about STEGLATRO (continued)

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported in patients with type 1 and type 2 diabetes receiving SGLT2 inhibitors including STEGLATRO. Some cases were fatal. Assess patients with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If ketoacidosis is suspected, STEGLATRO should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Before initiating STEGLATRO, consider risk factors for ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with STEGLATRO, consider monitoring for ketoacidosis and temporarily discontinuing

STEGLATRO in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

STEGLATRO causes intravascular volume contraction and can cause renal impairment. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors. Before initiating STEGLATRO, consider factors that may predispose patients to acute kidney injury. Consider temporarily discontinuing STEGLATRO in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue STEGLATRO promptly and institute treatment.

STEGLATRO increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) may be more susceptible to these changes. Renal function abnormalities can occur after initiating STEGLATRO. Renal function should be evaluated prior to initiating STEGLATRO and periodically thereafter. Use of STEGLATRO is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m².

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. Cases of pyelonephritis also have been reported in patients treated with STEGLATRO in clinical trials. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

An increased risk for lower limb amputation has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials with STEGLATRO, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the STEGLATRO 5 mg group, and 8 (0.5%) patients in the STEGLATRO 15 mg group. A causal association between STEGLATRO (ertugliflozin) and lower limb amputation has not been definitively established. Before initiating STEGLATRO, consider factors that may predispose patients to the need for amputations. Counsel patients about the importance of routine preventative foot care. Monitor patients and discontinue STEGLATRO if complications occur.

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. STEGLATRO may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLATRO.

STEGLATRO increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections. Monitor and treat appropriately.

Dose-related increases in low-density lipoprotein cholesterol (LDL-C) can occur with STEGLATRO. Monitor and treat as appropriate.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with STEGLATRO.

The most common adverse reactions associated with STEGLATRO (incidence $\geq 5\%$) were female genital mycotic infections.

Selected Important Risk Information about STEGLUJAN (ertugliflozin and sitagliptin) (continued)

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. After initiating STEGLUJAN, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, STEGLUJAN should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using STEGLUJAN.

Ertugliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating STEGLUJAN, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients (≥ 65 years), in patients with low systolic blood pressure, and in patients on diuretics. Before initiating STEGLUJAN, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms after initiating therapy.

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported in patients with type 1 and type 2 diabetes receiving SGLT2 inhibitors, including STEGLUJAN. Some cases were fatal. Assess patients with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If ketoacidosis is suspected, STEGLUJAN should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Before initiating STEGLUJAN (ertugliflozin and sitagliptin), consider risk factors for ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with STEGLUJAN, consider monitoring for ketoacidosis and temporarily discontinuing STEGLUJAN in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

STEGLUJAN causes intravascular volume contraction and can cause renal impairment. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors. Before initiating STEGLUJAN, consider factors that may predispose patients to acute kidney injury, including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications. Consider temporarily discontinuing STEGLUJAN in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue STEGLUJAN promptly and institute treatment.

Ertugliflozin increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) may be more susceptible to these changes. Renal function abnormalities can occur. Renal function should be evaluated prior to initiating STEGLUJAN and periodically thereafter. Use of STEGLUJAN is not recommended

when eGFR is persistently between 30 and less than 60 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m².

Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been identified in patients receiving SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly.

An increased risk for lower limb amputation has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials with ertugliflozin, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group. A causal association between ertugliflozin and lower limb amputation has not been definitively established. Before initiating STEGLUJAN, consider factors that may predispose patients to the need for amputations. Counsel patients about the importance of routine preventative foot care. Monitor patients and discontinue STEGLUJAN if complications occur.

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of STEGLUJAN prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients to report any symptoms of heart failure. If heart failure develops, evaluate and manage appropriately, and consider discontinuation of STEGLUJAN (ertugliflozin and sitagliptin).

STEGLUJAN may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Consider lowering the dose of these agents when coadministered with STEGLUJAN.

Ertugliflozin increases the risk of genital mycotic infections, particularly in patients with a history of these infections or who are uncircumcised. Monitor and treat appropriately.

Serious hypersensitivity reactions (anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome) have been reported in patients treated with sitagliptin. If a hypersensitivity reaction is suspected, discontinue STEGLUJAN, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor.

Dose-related increases in LDL-C can occur with STEGLUJAN.

Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients

experienced relief of symptoms upon discontinuation of medication. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous pemphigoid requiring hospitalization has been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report any development of blisters or erosions. If bullous pemphigoid is suspected, discontinue STEGLUJAN and consider referral to a dermatologist.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with STEGLUJAN.

The most common adverse reactions associated with ertugliflozin (incidence $\geq 5\%$) were female genital mycotic infections. The most common adverse reactions with sitagliptin (incidence $\geq 5\%$) were upper respiratory tract infection, nasopharyngitis, and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was more commonly reported in patients treated with sitagliptin.

Selected Important Risk Information about SEGLUROMET (ertugliflozin and metformin hydrochloride)

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio and metformin plasma levels generally >5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

If metformin-associated lactic acidosis is suspected, immediately discontinue SEGLUROMET (ertugliflozin and metformin hydrochloride) and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue SEGLUROMET and promptly notify their health care provider.

Recommendations to reduce the risk include:

- Renal Impairment: Obtain an estimated eGFR prior to initiating therapy and annually or more frequently in patients at increased risk of developing renal impairment.
- Drug Interactions: More frequent monitoring is recommended when administered with drugs that impair renal function, result in hemodynamic change, interfere with acid-base balance, or increase metformin accumulation.
- Age 65 or Greater: Assess renal function more frequently.
- Radiological Studies with Contrast: Stop SEGLUROMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR of less than 60 mL/min/1.73 m²; patients with a history of hepatic impairment, alcoholism, or heart failure; or patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the procedure and restart SEGLUROMET if renal function is stable.
- Surgery and Other Procedures: Discontinue while patients have restricted food and fluid intake.
- Hypoxic States: Discontinue in conditions associated with hypoxemia.
- Excessive Alcohol Intake: Warn patients against excessive alcohol intake.
- Hepatic Impairment: Avoid use in patients with evidence of hepatic disease.

Ertugliflozin causes intravascular volume contraction and symptomatic hypotension may occur after initiating SEGLUROMET, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients (≥65 years), or patients on diuretics. Before initiating SEGLUROMET (ertugliflozin and metformin hydrochloride), assess and correct volume status. Monitor for hypotension.

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported in patients with type 1 and type 2 diabetes receiving SGLT2 inhibitors, including ertugliflozin. Some cases were fatal. Assess patients with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If ketoacidosis is suspected, SEGLUROMET should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Before initiating SEGLUROMET, consider risk factors for ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with SEGLUROMET, consider monitoring for ketoacidosis and temporarily discontinuing SEGLUROMET in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

SEGLUROMET causes intravascular volume contraction and can cause renal impairment. There have been reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors. Before initiating SEGLUROMET, consider factors that may predispose patients to acute kidney injury. Consider temporarily discontinuing SEGLUROMET in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue SEGLUROMET promptly and institute treatment.

SEGLUROMET increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) may be more susceptible to these changes. Renal function abnormalities can occur after initiating SEGLUROMET. Renal function should be evaluated prior to initiating SEGLUROMET and periodically thereafter. Use of

SEGLUROMET is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m².

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate for urinary tract infections and treat promptly.

An increased risk for lower limb amputation has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials with ertugliflozin, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group. A causal association between ertugliflozin and lower limb amputation has not been definitively established. Before initiating SEGLUROMET, consider factors that may predispose patients to the need for amputations. Counsel patients about the importance of routine preventative foot care. Monitor patients and discontinue SEGLUROMET (ertugliflozin and metformin hydrochloride) if complications occur.

Ertugliflozin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Consider lowering the dose of these agents when coadministered with SEGLUROMET. Hypoglycemia could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation or during concomitant use of other glucose-lowering agents or with the use of ethanol.

Ertugliflozin increases the risk of genital mycotic infections, particularly in patients with a history of these infections or who are uncircumcised. Monitor and treat appropriately.

Dose-related increases in LDL-C can occur with SEGLUROMET. Monitor and treat as appropriate.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SEGLUROMET.

The most common adverse reactions associated with ertugliflozin (incidence $\geq 5\%$) were female genital mycotic infections. The most common adverse reactions associated with metformin (incidence $\geq 5\%$) were diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia and headache.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate

our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

About Pfizer Inc.: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2016 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Pfizer Disclosure Notice

The information contained in this release is current as of December 22, 2017. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about STEGLATRO (ertugliflozin), STEGLUJAN (ertugliflozin and sitagliptin) and SEGLUROMET (ertugliflozin and metformin hydrochloride), including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of STEGLATRO, STEGLUJAN and SEGLUROMET; the uncertainties inherent in research and development, including the ability to meet anticipated clinical trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; whether and when applications for STEGLATRO, STEGLUJAN, and SEGLUROMET may be filed in any other jurisdictions; whether and when any such other applications for STEGLATRO, STEGLUJAN and SEGLUROMET that may be pending or filed may be approved by regulatory authorities, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of STEGLATRO, STEGLUJAN, and SEGLUROMET; and competitive developments. The competitive landscape for type 2 diabetes therapies, including SGLT2 inhibitors, continues to evolve. The success of our ertugliflozin program is dependent on developments in that space.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

Please see Prescribing Information for STEGLATRO at

http://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf and Patient Information for STEGLATRO at http://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_mg.pdf

Please see Prescribing Information for STEGLUJAN at

http://www.merck.com/product/usa/pi_circulars/s/steglujan/steglujan_pi.pdf and Patient Information for STEGLUJAN at

http://www.merck.com/product/usa/pi_circulars/s/steglujan/steglujan_mg.pdf

Please see Prescribing Information for SEGLUROMET (ertugliflozin and metformin hydrochloride) at

http://www.merck.com/product/usa/pi_circulars/s/segluromet/segluromet_pi... and Patient Information for SEGLUROMET at

http://www.merck.com/product/usa/pi_circulars/s/segluromet/segluromet_mg...

PATIENT INFORMATION

JARDIANCE

®

(jar DEE ans)

(empagliflozin)

Tablets

What is the most important information I should know about JARDIANCE?

JARDIANCE can cause serious side effects, including:

-

Dehydration.

JARDIANCE can cause some people to have dehydration (the loss of body water and salt).

Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). You may be at higher risk of dehydration if you:

- have low blood pressure

- take medicines to lower your blood pressure including diuretics (water pills) ,

- are on low sodium (salt) diet

- have kidney problems

- are 65 years of age or older

-

Vaginal yeast infection.

Women who take JARDIANCE may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:

- vaginal odor white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)

- vaginal itching

-

Yeast infection of the penis (balanitis or balanoposthitis).

- Men who take JARDIANCE may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis.

- Other symptoms of yeast infection of the penis include: redness, itching, or swelling of the penis rash of the penis

- foul smelling discharge from the penis

- pain in the skin around penis

- Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina

- or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is JARDIANCE?

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JARDIANCE is a prescription medicine used: along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

to reduce the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.

-

JARDIANCE is not for people with type 1 diabetes.

-

JARDIANCE is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).

-

It is not known if JARDIANCE is safe and effective in children under 18 years of age.

Who should not take JARDIANCE?

Do not take JARDIANCE if you:

- are allergic to empagliflozin or any of the ingredients in JARDIANCE. See the end of this leaflet for a list of ingredients in JARDIANCE.
- have severe kidney problems or are on dialysis

What should I tell my doctor before using JARDIANCE?

Before you take JARDIANCE, tell your doctor if you:

- have kidney problems
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking)
- have any other medical conditions
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. If you become pregnant while taking JARDIANCE, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.

34

- are breastfeeding or plan to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby.

Talk with your doctor about the best way to feed your baby

if you are taking JARDIANCE. Do not breastfeed while taking JARDIANCE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

JARDIANCE may affect the way other medicines work, and other medicines may affect how JARDIANCE works.

Especially tell your doctor if you take:

- diuretics (water pills)

- insulin or other medicines that can lower your blood sugar

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

How should I take JARDIANCE?

- Take JARDIANCE exactly as your doctor tells you to take it.
- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.

-
- Your doctor may change your dose if needed.

If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule.

Do not take two doses of JARDIANCE at the same time. Talk with your doctor if you have questions about a missed dose.

-
- Your doctor may tell you to take JARDIANCE along with other diabetes medicines. Low blood sugar can happen more often when JARDIANCE is taken with certain other diabetes medicines.

See "What are the possible side effects of JARDIANCE?"

-
- If you take too much JARDIANCE, call your doctor or go to the nearest hospital emergency room right away.

When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.

-
- Check your blood sugar as your doctor tells you to.

Stay on your prescribed diet and exercise program while taking JARDIANCE.

-
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.

Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin HbA1c.

-
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test. What are the possible side effects of JARDIANCE?

JARDIANCE may cause serious side effects, including:

-
- See "What is the most important information I should know about JARDIANCE?"

Ketoacidosis (increased ketones in your blood or urine).

Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with JARDIANCE. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death.

Ketoacidosis can happen with JARDIANCE even if your blood sugar is less than 250 mg/dL.

Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms

0

nausea

0

tiredness

0

vomiting

0

trouble breathing

0

stomach-area (abdominal) pain

If you get any of these symptoms during treatment with JARDIANCE, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

-

Serious urinary tract infections.

Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine.

Sometimes people also may have a fever, back pain, nausea or vomiting.

-

Low blood sugar (hypoglycemia).

If you take JARDIANCE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JARDIANCE. Signs and symptoms of low blood sugar may include:

- o

headache

- o

irritability

- o

confusion

- o

dizziness

- o

drowsiness

- o

hunger

- o

shaking or feeling jittery

- o

sweating

Why Has Your Physician Prescribed Welchol?

Welchol[®] (colesevelam HCl) is a prescription medication that, along with diet and exercise, can be used to improve blood glucose control in adults with type 2 diabetes who are on certain other anti-diabetic medications for blood glucose. Welchol can also be used along with diet and exercise for people whose LDL-C, the "bad" cholesterol, is too high.

Your physician may prescribe Welchol together with certain other type 2 diabetes medicines to help control blood glucose. When added to metformin, a sulfonylurea, or insulin, Welchol further reduces blood glucose levels.

Welchol can also be prescribed alone or with other cholesterol-lowering medications to lower LDL-C. When used with a statin, Welchol helps lower LDL-C more than a statin alone.

How to Take Welchol

Welchol[®] (colesevelam HCl) should be taken as directed by your physician. Welchol is dosed at 6 tablets per day (either as 3 tablets twice daily, or 6 tablets once daily, taken with meals and a liquid).

Although 6 pills may seem like a lot, keep in mind that Welchol is a safe way to effectively lower your blood glucose and/or bad cholesterol. Unlike other type 2 diabetes or cholesterol medications, Welchol does not enter your bloodstream. Your liver or kidneys are not needed to make Welchol work or to remove Welchol from your body. Taking Welchol as prescribed by your physician gives you an opportunity to help reach your blood glucose and/or LDL-C goal.

Important Information About Welchol

Welchol lowers LDL or "bad" cholesterol along with diet and exercise. It can be taken alone or with other cholesterol-lowering medications known as statins.

Welchol, along with diet and exercise, also lowers blood sugar levels in patients with type 2 diabetes mellitus when added to other antidiabetic medications (metformin, sulfonylureas, or insulin).

Ask your doctor if Welchol is right for you.

Welchol is not for everyone, especially those with intestinal blockage, those with blood triglyceride levels of greater than 500 mg/dL, or a history of pancreatitis (inflammation of the pancreas) due to high triglyceride levels.

Welchol has not been shown to prevent heart disease or heart attacks.

Tell your doctor if you have high triglycerides (greater than 300 mg/dL).

Tell your doctor if you have stomach or intestinal problems, including gastroparesis (when the stomach takes too long to empty its contents), abnormal contractions of the digestive system, major gastrointestinal tract surgery, if you have trouble swallowing, or if you have vitamin A, D, E, or K deficiencies.

Welchol has known interactions with glyburide (a drug for diabetes), levothyroxine (a drug used to treat an underactive thyroid) and certain oral contraceptives. Welchol has not been studied with all combinations of drugs and supplements. Please tell your doctor about all medications and supplements you may be taking before beginning Welchol, as your doctor may tell you to take your other medications and supplements 4 hours before taking Welchol.

Remember to tell your doctor if you are pregnant, plan to become pregnant, or are breastfeeding.

In patients with high LDL ("bad" cholesterol) side effects that occurred greater than placebo (a "sugar" pill) were constipation (11.0% vs. 7.0%), indigestion (8.3% vs. 3.5%), nausea (4.2% vs. 3.9%), accidental injury (3.7% vs. 2.7%), weakness (3.6% vs. 1.9%), sore throat (3.2% vs. 1.9%), flu-like symptoms (3.2% vs. 3.1%), runny nose (3.2% vs. 3.1%) and muscle aches (2.1% vs. 0.4%).

In patients with Type 2 Diabetes side effects that occurred greater than placebo were constipation (8.7% vs. 2.0%), inflamed nasal passages and throat (4.1% vs. 3.6%), indigestion (3.9% vs. 1.4%), low blood sugar (3.0% vs. 2.3%), nausea (3.0% vs. 1.4%) and high blood pressure (2.8% vs. 1.6%).

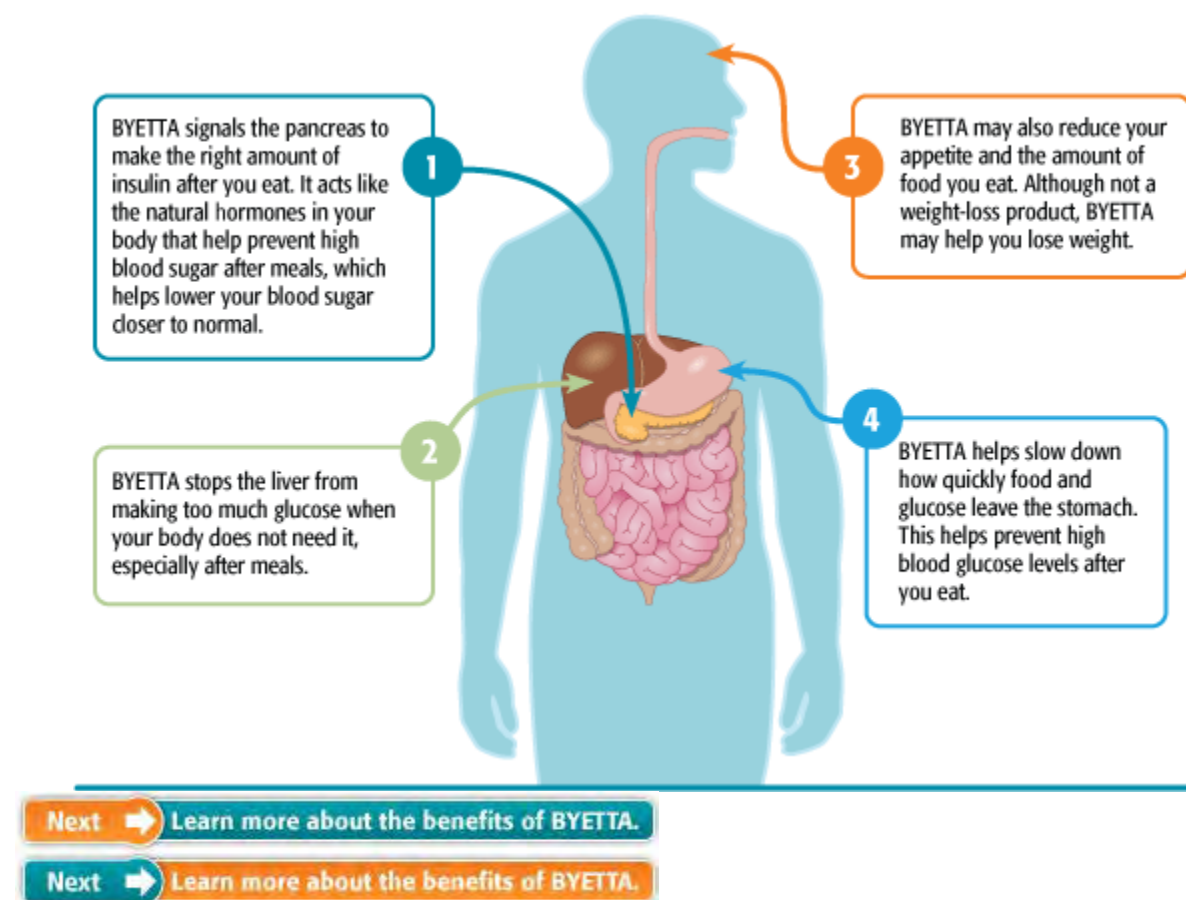
The content provided herein is for informational purposes only and does not constitute or substitute for professional medical advice, diagnosis, or treatment. Talk to your doctor for more information about your specific condition.

How BYETTA Works

In people with **type 2 diabetes**, high **blood sugar (glucose)** is a big concern. After a meal, **blood sugar levels** rise, often too high. BYETTA slows down the rate at which glucose enters the bloodstream. BYETTA signals the **pancreas** to make the right amount of **insulin** at the right time to help blood sugar remain closer to normal.

After blood sugar levels off, BYETTA stops signaling the pancreas to produce insulin. This effect helps the body avoid low blood sugar, too (called **hypoglycemia**). As a result, BYETTA may help reduce your high blood sugar levels throughout the day. And that can mean better control, which can be one of the keys to helping manage your diabetes.

BYETTA is not insulin and should not be taken instead of insulin. BYETTA actually helps your body make more of its own insulin. When used with a diet and exercise program, BYETTA can help keep your blood sugar under control in at least four ways:



Indication

BYETTA is an injectable prescription medicine that may improve blood sugar (glucose) control in adults with type 2 diabetes mellitus, when used with a diet and exercise program.

BYETTA is not insulin and should not be taken instead of insulin. BYETTA can be used with Lantus® (insulin glargine), which is a long-acting insulin, but should not be taken with short- and/or rapid-acting insulin. BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis.

Important Safety Information for BYETTA® (exenatide) injection

- Serious side effects can happen in people who take BYETTA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Before taking BYETTA, tell your healthcare provider if you have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels. Call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting and may be felt going from your abdomen through to your back.
- Your risk for getting low blood sugar is higher if you take BYETTA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. The dose of your sulfonylurea or insulin medicine may need to be lowered while you use BYETTA.
- BYETTA should not be used in people who have severe kidney problems and should be used with caution in people who have had a kidney transplant. BYETTA may cause new or worse problems with kidney function, including kidney failure.
- Before you use BYETTA, tell your healthcare provider if you have severe problems with your stomach, such as delayed emptying of your stomach (gastroparesis) or problems with digesting food.
- Do not use BYETTA if you have had an allergic reaction to exenatide or any of the other ingredients in BYETTA. Severe allergic reactions can happen with BYETTA. Stop taking BYETTA and get medical help right away.
- Tell your healthcare provider if you are pregnant or plan to become pregnant. It is not known if BYETTA will harm your unborn baby. Talk to your healthcare provider first if you are breastfeeding or plan to breastfeed.
- The most common side effects with BYETTA include nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, acid stomach, constipation, and weakness. Nausea most commonly happens when first starting BYETTA, but may become less over time.

These are not all the side effects with BYETTA. Talk to your healthcare provider about any side effect that bothers you or that does not go away.

How Victoza® works

If you have type 2 diabetes, your doctor or diabetes care team may have told you that your body may not produce enough [insulin](#) or your body may not respond to the insulin it makes. Insulin helps the sugar in the food you eat move from your blood into your cells.

GLP-1 Is a Hormone That Helps Lower Blood Sugar

If your body is not making enough of a [hormone](#) called [GLP-1](#) or not using it correctly, then you may not be getting the right amount of insulin to help sugar make the transition from the blood to the cells.

Victoza® Is 97% Similar to GLP-1, a Natural Hormone Made in Your Body

By acting like GLP-1, Victoza® helps make more insulin available in your blood to help lower your blood sugar levels quickly. This hormone is released from your small intestine when you eat—and can slow down the process of food leaving your stomach, which helps control your blood sugar levels.

Victoza® Helps Beta Cells Work the Way They Should

GLP-1 triggers important cells in your [pancreas](#), called [beta cells](#), to make insulin when your blood sugar is too high. This is important because, over time, beta cells stop working in people with type 2 diabetes. By the time of diagnosis, about 50% of beta cells are no longer working the way they should.

Victoza® Is Not Insulin

Victoza® is taken once a day by injection. It does not contain [insulin](#) and should not be taken with insulin. Victoza® may be taken alone or in combination with one or more common oral type 2 diabetes medications, including [biquanides \(such as metformin\)](#), [sulfonylureas \(SUs\)](#), or [thiazolidinediones \(TZDs\)](#).

Indications and Usage

Victoza® (liraglutide [rDNA origin] injection) is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes when used along with diet and exercise.

Victoza® is not recommended as the first medication to treat diabetes. Victoza® has not been studied in patients with history of inflammation of the pancreas (pancreatitis). Victoza® is not a substitute for insulin and has not been studied in combination with prandial (mealtime) insulin. Victoza® is not for people with type 1 diabetes or people with diabetic ketoacidosis. It is not known if Victoza® is safe and effective in children. Victoza® is not recommended for use in children.

Important Safety Information

In animal studies, Victoza® caused thyroid tumors—including thyroid cancer—in some rats and mice. It is not known whether Victoza® causes thyroid tumors or a type of thyroid

cancer called medullary thyroid cancer (MTC) in people, which may be fatal if not detected and treated early. Do not use Victoza® if you or any of your family members have a history of MTC or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). While taking Victoza®, tell your doctor if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.

Do not use Victoza® if you are allergic to liraglutide or any of the ingredients in Victoza®. Serious allergic reactions can happen with Victoza®. If symptoms of serious allergic reactions occur, stop taking Victoza® and seek medical attention. Pancreatitis may be severe and lead to death. Before taking Victoza®, tell your doctor if you have had pancreatitis, gallstones, a history of alcoholism, or high blood triglyceride levels since these medical conditions make you more likely to get pancreatitis.

Stop taking Victoza® and call your doctor right away if you have pain in your stomach area that is severe and will not go away, occurs with or without vomiting, or is felt going from your stomach area through to your back. These may be symptoms of pancreatitis.

Before using Victoza®, tell your doctor about all the medicines you take, especially sulfonylurea medicines or insulin, as taking them with Victoza® may affect how each medicine works. If you use Victoza® with insulin, you may give both injections in the same body area (for example, your stomach area), but not right next to each other.

Also tell your doctor if you have severe stomach problems such as slowed emptying of your stomach (gastroparesis) or problems with digesting food; have or have had kidney or liver problems; have any other medical conditions; or are pregnant or plan to become pregnant. Tell your doctor if you are breastfeeding or plan to breastfeed. It is unknown if Victoza® will harm your unborn baby or if Victoza® passes into your breast milk.

Your risk for getting hypoglycemia, or low blood sugar, is higher if you take Victoza® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. The dose of your sulfonylurea medicine or insulin may need to be lowered while taking Victoza®.

Victoza® may cause nausea, vomiting, or diarrhea leading to dehydration, which may cause kidney failure. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration.

The most common side effects with Victoza® include headache, nausea, and diarrhea. Nausea is most common when first starting Victoza®, but decreases over time in most people. Immune system related reactions, including hives, were more common in people treated with Victoza® compared to people treated with other diabetes drugs in medical studies.

Another Positive CV Outcomes Trial for Diabetes Drug: SUSTAIN-6

Lisa Nainggolan

|September 16, 2016

MUNICH — A second glucagonlike-peptide 1 (GLP-1) agonist has shown positive results in a major cardiovascular-outcomes trial in type 2 diabetes patients at high risk of cardiovascular disease.

Patients treated with one of two doses of the investigational agent semaglutide (Novo Nordisk), which has a long half-life and only needs to be injected subcutaneously once a week, had a significant 26% lower risk of the primary composite outcome of first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke over 2 years compared with those receiving placebo in the [SUSTAIN-6](#) trial, reported here at the [European Association for the Study of Diabetes \(EASD\) 2016 Annual Meeting](#) today.

Semaglutide was also a potent glucose-lowering agent, with significant and sustained reductions in HbA_{1c} levels seen with the agent, as compared with placebo, and similar rates of hypoglycemia, although glucose lowering was not the main point of the trial.

The lower cardiovascular risk was principally driven by a significant 39% decrease in nonfatal stroke and a 26% reduction in nonfatal MI (nonsignificant); there was no difference in cardiovascular deaths between the different arms of the trial — 0.5 mg of semaglutide once weekly, 1.0 mg of semaglutide once weekly, and corresponding placebo groups.

And the number of patients who would need to be treated to prevent one event of the primary outcome over 2 years was 45.

The main results of the 3200-patient trial conducted in 22 countries were reported by the principal investigator, cardiologist Steven P Marso, MD, of the Research Medical Center, Kansas City, Missouri, to applause from a packed convention hall and were simultaneously published online in the *New England Journal of Medicine*.

Cardiologist Dr Lars Rydén, from Karolinska University Hospital, Stockholm, Sweden, who was not involved in the SUSTAIN-6 trial but was the designated discussant at the meeting, said the reduction in cardiovascular events seen with semaglutide in the trial "is quite substantial and better than" is seen in some studies of cardiology agents — for example, platelet-stabilizing drugs.

However, he noted that the separation of curves "takes some time, around a year and a half, but from then on [the benefit] expands." Given that the primary end point was driven by nonfatal stroke and to a lesser extent MI, but not by death, and that hospitalization for heart failure was not affected, the effect of semaglutide is likely on atherosclerosis, he noted.

Regarding the lack of a reduction in cardiovascular deaths with semaglutide in the study, Dr Rydén told *Medscape Medical News*: "It takes time for cardiovascular benefits to translate into mortality — it's only 2.1 years [trial duration]. They had enough events to show what they wanted, but it's still a very short period in the life of people with diabetes."

There was a concern about higher rates of retinopathy complications in those receiving semaglutide. Vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation were

significantly higher among those receiving semaglutide, occurring in 3% of patients on the active drug compared with 1.8% of the placebo group, a 76% increase ($P = .02$).

Presenting this finding as part of the clinical and metabolic outcomes of the study, endocrinologist Tina Vilsbøll, MD, DMSc, of the Center for Diabetes Research, Gentofte Hospital, Copenhagen, Denmark, said: "This is the only forest plot that goes in the wrong direction."

However, she pointed out, "The signals we saw were mostly only in patients with retinopathy at baseline." Nevertheless, she noted that there is an association between rapid glucose lowering and retinopathy — as seen in the [DCCT](#) trial—and this observation requires further investigation.

Asked to comment on the findings for *Medscape Medical News*, endocrinologist Bernie Zinman, MDCM, FRCPC, FACP, from Mount Sinai Hospital, Toronto, Ontario, stressed that "the retinal outcomes [in SUSTAIN-6] can't be ignored; it's a small number of events, but [[Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation](#)] LEADER also had it going in that direction, so I think that has to be further evaluated to determine whether it's real or not."

"Is it just a worsening of retinopathy when you have rapid improvement and control [of glucose]? Or is there a biological effect on the eye? It remains to be seen."

Wonderful Era for Diabetes — GLP-1 Agonist/SGLT-2 Inhibitor Combos?

Semaglutide joins another Novo Nordisk GLP-1 agonist, liraglutide (*Victoza*), which in June demonstrated cardiovascular benefit when added to standard of care in type 2 diabetes patients at high cardiovascular risk in the LEADER trial.

LEADER was the second such [mandated FDA cardiovascular safety study](#) for a diabetes drug to show cardiovascular benefit, rather than just lack of harm, on top of standard therapy in type 2 diabetes patients at high cardiovascular risk, after the [EMPA-REG](#) trial, and the first with an agent from the GLP-1 receptor agonist class.

EMPA-REG was the first trial to show a reduction in cardiovascular death with a glucose-lowering drug, the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (*Jardiance*/Boehringer Ingelheim/Lilly), a different class of contemporary diabetes agent, and this study was [reported](#) a year ago, at the EASD meeting in 2015.

Importantly, these two classes of glucose-lowering agents, GLP-1 agonists and SGLT2 inhibitors, seem to be reducing cardiovascular events via different mechanisms — the GLP-1 agonists via a delay in the progression of atherosclerosis while the SGLT2 inhibitors appear to be preventing heart failure and associated deaths.

Commenting on how the landscape now looks for contemporary diabetes drugs, Dr Zinman — who was an investigator for the EMPA-REG trial — told *Medscape Medical News*: "We are in a wonderful era of diabetes. We have drugs that don't cause hypoglycemia or weight gain, and they work very effectively. They can be used in combination — and I think they should be — and one has to study whether together they will be even better."

Regarding SUSTAIN-6 specifically, Dr Zinman said: "It's exciting to have another positive trial with respect to cardiovascular outcomes. What was prominent was the very robust effect in reducing the primary outcome in a small number of patients over a short period of time. And despite everybody treating to target, the HbA_{1c}

difference was substantial [between semaglutide and placebo], so this is a very potent drug that lowers A_{1c} very well."

"Endocrinologists and primary-care physicians are going to be happy that we now have opportunities to use agents that can reduce cardiovascular outcomes," he observed.

But, "as with all trials, new questions are raised," Dr Zinman pointed out. "It's a little bit of a disappointment that there was no change in cardiovascular death, whereas with LEADER there was," and he reiterated the further work required to determine whether the retinopathy signal should be of concern or not.

Dr Rydén told *Medscape Medical News*: "GLP-1 receptor agonists are now shown in two major trials to be not only safe but efficient for glucose lowering, avoiding hypoglycemia, and reducing weight, so they are an ideal drug to use, for instance, with insulin."

"Meanwhile, we have to see whether the heart-failure protecting drug, empagliflozin, and [GLP-1 agonist] together will be something even better," he added.

And he has another message for endocrinologists: "Why should we ever use a sulfonylurea anymore? There are many observational and registry studies showing that sulfonylurea as an addition to metformin is perhaps not a very good choice."

SUSTAIN-6 Cardiovascular Outcomes

In SUSTAIN-6, 3297 patients with type 2 diabetes and an HbA_{1c} of 7% or more aged at least 50 were randomized. Of them, 2735 had established cardiovascular disease, chronic kidney disease, or both; the remainder were aged at least 60 with at least one cardiovascular risk factor. Mean duration of diabetes was 13.9 years and mean HbA_{1c} was 8.7%.

Most patients (93.5%) were taking antihypertensive medication, 76.5% were receiving lipid-lowering drugs, and 76.3% were receiving antithrombotic medications.

The trial is the first preapproval study to demonstrate cardiovascular safety of a potential agent for diabetes, as per the FDA requirement of 2008, and was conducted between February 2013 and December 2013.

A fixed-dose escalation procedure was used, with a starting dose of 0.25 mg of semaglutide (or corresponding placebo) for 4 weeks that escalated to 0.5 mg for 4 weeks until the maintenance dose (0.5 mg or 1.0 mg) was reached. No change in the maintenance dose of either semaglutide or placebo was permitted for the duration of the trial.

Dr Marso noted the cardiovascular risk reduction seen with semaglutide occurred early "and extended and diverged over time," despite the fact an increase in pulse rate of 2 beats per minute was seen with the active drug compared with placebo.

Similar risk reductions were observed with both doses of semaglutide, so they were combined for analysis purposes.

Throughout the trial, a greater proportion of patients in the placebo group than the semaglutide group received additional cardiovascular medications, Dr Marso noted.

"The reduction in CV events observed with semaglutide in SUSTAIN-6 is notable, given the small study population and the short duration," he concluded.

"These findings are clinically relevant, as CVD is the leading cause of death in people with type 2 diabetes, and new treatment options that can also reduce the risk of CV events are needed."

Primary and Secondary Cardiovascular and Microvascular Outcomes

Outcome	Semaglutide, n=1648 (%)	Placebo, n=1649 (%)	Hazard ratio	P
Primary composite outcome*	6.6	8.9	0.74	< .001 for noninferiority; 0.02 for superiority
Death from any cause	3.8	3.6	1.05	0.79
CV death	2.7	2.8	0.98	0.92
Nonfatal MI	2.9	3.9	0.74	0.12
Nonfatal stroke	1.6	2.7	0.61	0.04
Revascularization	5.0	7.6	0.65	0.003
Hospitalization for HF	3.6	3.3	1.11	0.57
Retinopathy complications	3.0	1.8	1.76	0.02
New or worsening nephropathy	3.8	6.1	0.64	0.005

Glucose Lowering, Other Clinical Outcomes, and Safety

Dr Vilsbøll documented the "sustained effect" of semaglutide, with respect to HbA_{1c} and fasting plasma glucose. From an overall baseline of 8.7%, semaglutide significantly reduced HbA_{1c} by 1.4% and 1.1% (for the two doses) vs 0.4% for placebo.

"So 39% of patients on the 0.5-mg dose of semaglutide and 49% of those on 1.0-mg dose achieved the ADA target of HbA_{1c} < 7.0%," she noted, and a higher proportion of patients receiving placebo had to intensify their [other] antihyperglycemic treatment.

Rates of hypoglycemia didn't differ between the active and placebo groups, either, she noted.

Body weight "decreased by almost 5 kg with the 1.0-mg dose of semaglutide, from a mean of 92.1 kg," compared with weight loss of 3.6 kg, on average, in the 0.5-mg group and 0.5 to 0.7 kg in the placebo recipients.

Meanwhile, Lawrence Leiter, MD, FRCP, director of the lipid clinic at St Michael's Hospital, Toronto, Ontario, presented the safety findings from SUSTAIN-6 and noted that the total number of adverse events was comparable between all groups, and few serious adverse events were seen with semaglutide. As would be expected, the most common side effects with the active drug were gastrointestinal in nature; nausea, vomiting, and diarrhea, and treatment discontinuation for these reasons was more frequent with semaglutide.

Pancreatitis occurred in low and similar numbers in both active-drug and placebo groups, and the frequency and rate of malignant neoplasms was also similar between all arms.

Dr Vilsbøll discussed the retinopathy outcomes in more detail — the majority of subjects who developed diabetic retinopathy complications (> 80%) had preexisting retinopathy at baseline, she stressed.

Specifically, 38 patients taking semaglutide needed retinal photocoagulation vs 20 on placebo; 16 had a vitreous hemorrhage vs seven; while 16 required treatment with intravitreal agents compared with 13 on placebo; and five of those taking semaglutide experienced the onset of diabetes-related blindness, compared with one in the placebo group.

"We have to look into this more; I don't have the exact explanation of why that is, but the numbers were overall small," Dr Vilsbøll told *Medscape Medical News*.

In contrast, there was a "very nice effect" of semaglutide on nephropathy, she noted.

In conclusion, she said: "It's great to see another trial with a GLP-1 agonist being positive. It is in a high-risk population, and we are not completely sure whether we'll see the same results in a broader population.

"But a risk reduction of 26% overall is really important for me as a diabetologist with this class. It might take a couple of years until we have this agent on the market, but it's good for the class, and it's good for the patient."

Dr Marso reports personal fees from Novo Nordisk during the conduct of the study; grant support and personal fees from Novo Nordisk, and personal fees from Abbott Vascular and AstraZeneca outside the submitted work. Dr Vilsbøll reports being an advisory board member for Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi and consulting or being a speaker for or receiving research support from AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen Cilag, MSD, Novo Nordisk, Sanofi, and Zealand Pharma. Dr Leiter is on the advisory panel and the speaker's bureau for and has received research support from AstraZeneca, as well as from other pharmaceutical companies. Disclosures for the coauthors are listed on the [journal website](#). Dr Rydén has no relevant financial relationships. Dr Zinman reports having served as a director, officer, partner, employee, advisor, consultant, or trustee for Eli Lilly, Boehringer Ingelheim, AstraZeneca, Merck, and Novo Nordisk and receiving research grants from Boehringer Ingelheim and Merck, and AstraZeneca.

Follow Lisa Nainggolan on Twitter: [@lisanainggolan1](#). For more diabetes and endocrinology news, follow us on [Twitter](#) and on [Facebook](#).

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How BYDUREON Works

BYDUREON Helps Your Body Make Insulin Only When It's Needed

BYDUREON (exenatide extended-release for injectable suspension) acts like a natural hormone that tells your body when to make its own insulin. Just as a thermostat senses rises in temperature, your body senses rises in blood sugar and BYDUREON works with your body to enhance its ability to release its own insulin, only at the times it's needed.

Here's what happens:

After you eat a meal, your blood sugar level usually goes up. When your body senses this rise in blood sugar, BYDUREON enhances your body's ability to release its own insulin.

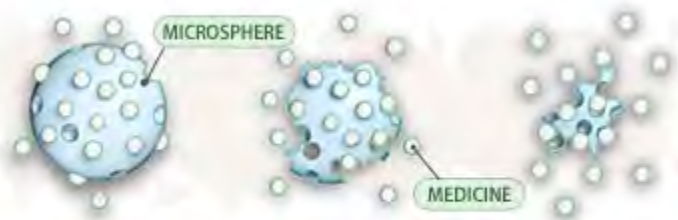
When your body senses your blood sugar has come down to the right level, the release of insulin slows.

Important Safety Information: Hypoglycemia

Your risk for getting low blood sugar (hypoglycemia) is higher if you take BYDUREON with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea may need to be lowered while you use BYDUREON. Signs and symptoms of low blood sugar may include shakiness, headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, and feeling jittery.

Just One Dose Lasts All Week Long

Each weekly dose of BYDUREON is made up of microspheres that hold the medicine. Over time the microspheres slowly dissolve, continuously releasing the medicine into your body over an entire week.



Close-up of a microsphere dissolving, continuously releasing medicine over time.

Next: Is BYDUREON Right for Me? ▶

WHAT IS BYDUREON® (exenatide extended-release for injectable suspension)?

BYDUREON is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise. BYDUREON is not recommended as the first medication to treat diabetes.

BYDUREON is a long-acting form of the medication in BYETTA® (exenatide) injection so both drugs should not be used together. BYDUREON is not a substitute for insulin and has not been studied in combination with insulin. BYDUREON is not for people with type 1 diabetes or people with diabetic ketoacidosis (a condition caused by very high blood sugar). BYDUREON is not recommended for use in children. It is not known if BYDUREON is safe and effective in people with a history of pancreatitis or severe kidney problems.

IMPORTANT SAFETY INFORMATION for BYDUREON

- **POSSIBLE THYROID TUMORS, INCLUDING CANCER:** In animal studies, BYDUREON caused rats to develop tumors of the thyroid gland. Some of these tumors were cancer. It is not known if BYDUREON causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in people. Do not take BYDUREON if you or any of your family members have MTC or if you have Multiple Endocrine Neoplasia syndrome type 2. While taking BYDUREON, tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.
- Do not take BYDUREON if you have had an allergic reaction to exenatide or any of the other ingredients in BYDUREON. Severe allergic reactions can happen with BYDUREON. Symptoms of a severe allergic reaction to BYDUREON are severe rash or itching, swelling of your face, lips, and throat that may cause difficulty breathing or swallowing, feeling faint or dizzy and very rapid heartbeat. If you have any symptoms of a severe allergic reaction, stop taking BYDUREON and call your healthcare provider right away.
- Inflammation of the pancreas (pancreatitis) may happen, which may be severe and lead to death. Before taking BYDUREON, tell your healthcare provider if you have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels. Stop taking BYDUREON and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away, occurs with or without vomiting, or is felt going from your stomach area through to your back. These may be symptoms of pancreatitis.
- Your risk for getting low blood sugar (hypoglycemia) is higher if you take BYDUREON with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea may need to be lowered while you use BYDUREON. Signs and symptoms of low blood sugar may include shakiness, headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, and feeling jittery.
- Tell your healthcare provider if you have or had kidney problems or a kidney transplant. BYDUREON may cause nausea, vomiting, or diarrhea, leading to loss of fluids (dehydration). Dehydration may cause kidney failure; this can happen in people who have never had kidney problems before. Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away or if you cannot drink liquids.
- Tell your healthcare provider if you have severe problems with your stomach, such as delayed emptying of your stomach (gastroparesis) or problems with digesting food.
- The most common side effects with BYDUREON include nausea, diarrhea, headache, vomiting, constipation, itching at injection site, a small bump (nodule) at the injection site, and indigestion. Nausea most commonly happens when first starting BYDUREON, but may become less over time.
- Before using BYDUREON, tell your doctor about all the medicines you take, as taking them with BYDUREON may affect how each medicine works. Tell your healthcare provider if you take other diabetes medicines, especially insulin or a sulfonylurea, or warfarin sodium (Coumadin® or Jantoven®).

- Tell your healthcare provider if you are pregnant or plan to become pregnant. It is not known if BYDUREON will harm your unborn baby. Talk to your healthcare provider first if you are breastfeeding or plan to breastfeed.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Medication Guide
TRULICITY™ (Trū-li-si-tee)
(dulaglutide)
injection, for subcutaneous use

Read this Medication Guide before you start using TRULICITY and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about TRULICITY?

Serious side effects may happen in people who use TRULICITY, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, medicines that work like TRULICITY caused thyroid tumors, including thyroid cancer. It is not known if TRULICITY will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people.
- Do not use TRULICITY if you or any of your family have ever had a type of thyroid cancer called medullary thyroid cancer (MTC), or if you have an endocrine system cancer called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is TRULICITY?

TRULICITY is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.

- TRULICITY is not recommended as the first choice of medicine for treating diabetes.
- It is not known if TRULICITY can be used in people who have had pancreatitis.
- TRULICITY is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- TRULICITY is not recommended in people with severe stomach or intestinal problems.
- It is not known if TRULICITY can be used with long-acting insulin.
- It is not known if TRULICITY is safe and effective in children.

Who should not use TRULICITY?

Do not use TRULICITY if:

- you or your family have ever had a type of thyroid cancer called medullary thyroid cancer (MTC) or if you have an endocrine system cancer called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are allergic to dulaglutide or any of the ingredients in TRULICITY. See the end of this Medication Guide for a complete list of ingredients in TRULICITY.

What should I tell my healthcare provider before using TRULICITY?

Before using TRULICITY, tell your healthcare provider if you:

- have or have had problems with your pancreas, kidneys or liver.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant or plan to become pregnant. It is not known if TRULICITY will harm your unborn baby. Tell your healthcare provider if you become pregnant while using TRULICITY.
- are breastfeeding or plan to breastfeed. It is not known if TRULICITY passes into your breast milk. You should not use TRULICITY while breastfeeding without first talking to your healthcare provider.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Before using TRULICITY, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes including insulin or sulfonylureas.

How should I use TRULICITY?

- Read the **Instructions for Use** that comes with TRULICITY.
- Use TRULICITY exactly as your healthcare provider tells you to.
- Your healthcare provider should show you how to use TRULICITY before you use it for the first time.
- TRULICITY is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject TRULICITY into a muscle (intramuscularly) or vein (intravenously).
- **Use TRULICITY 1 time each week on the same day each week at any time of the day.**
- You may change the day of the week as long as your last dose was given **3** or more days before.
- If you miss a dose of TRULICITY, take the missed dose as soon as possible if there are at least **3** days (72 hours) until your next scheduled dose. If there are less than **3** days remaining, skip the missed dose and take your next dose on the regularly scheduled day. **Do not** take **2** doses of TRULICITY within **3** days of each other.
- You can use TRULICITY with or without food.
- **Do not** mix insulin and TRULICITY together in the same injection.
- You may give an injection of TRULICITY and insulin in the same body area (such as, your stomach area), but not right next to each other.
- Change (rotate) injection site with each weekly injection. **Do not** use the same site for each injection.
- **Do not share your pen, syringe, or needles with another person.** You may give another person an infection or get an infection from them.

Your dose of TRULICITY and other diabetes medicines may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of TRULICITY?

TRULICITY may cause serious side effects, including:

- See “**What is the most important information I should know about TRULICITY?**”
- **inflammation of your pancreas (pancreatitis).** Stop using TRULICITY and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you take TRULICITY with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin.

Signs and symptoms of low blood sugar may include:

- dizziness or light-headedness
- blurred vision
- anxiety, irritability, or mood changes
- sweating
- slurred speech
- hunger
- confusion or drowsiness
- shakiness
- weakness
- headache
- fast heartbeat
- feeling jittery
- **allergic reactions.** Stop using TRULICITY and get medical help right away, if you have any symptoms of an allergic reaction including itching, rash, or difficulty breathing.
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- **severe stomach problems.** Other medicines like TRULICITY may cause severe stomach problems. It is not known if TRULICITY causes or worsens stomach problems.

Common side effects of TRULICITY may include nausea, diarrhea, vomiting, decreased appetite, and indigestion. These are not all the possible side effects of TRULICITY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRULICITY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRULICITY for a condition for which it was not prescribed. Do not give TRULICITY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about TRULICITY. If you would like more information, talk with your healthcare provider. You can ask your doctor or pharmacist for information about TRULICITY that is written for health professionals.

What are the ingredients in TRULICITY?

Active ingredient: dulaglutide

Inactive ingredients: citric acid anhydrous, mannitol, polysorbate 80 and trisodium citrate dehydrate

For more information go to www.TRULICITY.com or call 1-800-545-5979.

This Medication Guide has been approved by the U.S. Food and Drug Administration

TRULICITY is a registered trademark of Eli Lilly and Company.

Issued: SEP 2014

Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA, US License Number 1891

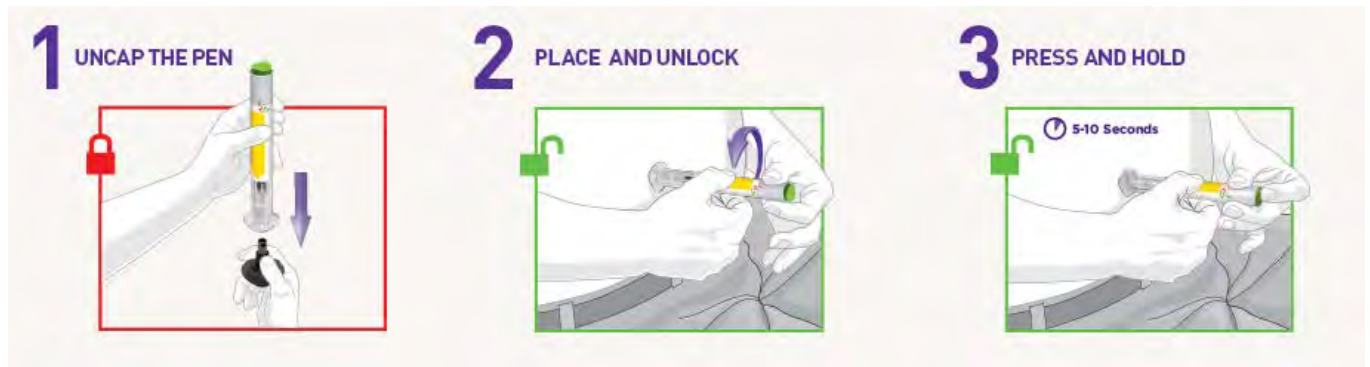
www.TRULICITY.com.

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TRU-0001-MG-20140918

Using your Trulicity pen.

Read the Instructions for Use included with your pen for more information on how to deliver your Trulicity dose.



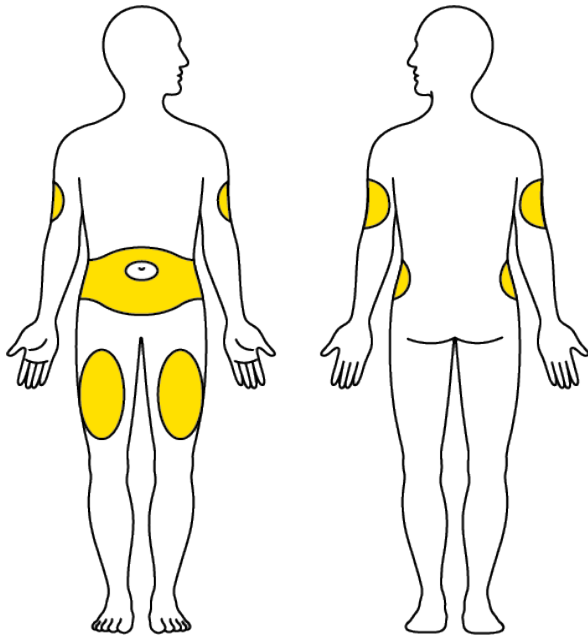
Storing and handling the Trulicity pen.

- Store your pen in the refrigerator, but do not freeze your pen. When refrigeration is not possible, you can keep your pen at room temperature (below 86°F, 30°C) for up to a total of 14 days
- Store Trulicity away from light. It's best to keep Trulicity pens in their original carton until you are ready to use them

For complete information about proper storage, read the [Instructions for Use](#).

Select a spot on your body.

- Your healthcare provider can help you choose the injection site that is best for you
- You may inject the medicine into your stomach (abdomen) or thigh
- Another person may give you the injection in your upper arm
- Change your injection site each week. You may use the same area of your body, but be sure to choose a different injection site in that area



Disposing of the pen.



Be sure to dispose of the pen in a closable, puncture-resistant container. Ask your healthcare provider about regulations in your area for how to dispose of the container properly.

[Click here for information about a free sharps container.](#)

What happens if you miss a dose?

It's a good idea to take Trulicity regularly on the same day of the week, every week. If you forget to take your dose on your usual day, here's what to do.

When to take your dose:

- Take the missed dose as soon as possible if there are at least 3 days (72 hours) until your next Trulicity day.

When to skip your dose:

- Skip the missed dose if there are less than 3 days remaining and take your next dose on your regularly scheduled Trulicity day. Do not take 2 doses of Trulicity within 3 days of each other.

Indication and Limitations of Use: Trulicity is a once-weekly injectable prescription medicine to improve blood sugar (glucose) in adults with type 2 diabetes mellitus. It should be used along with diet and exercise. Trulicity is not recommended as the first medication to treat diabetes. It has not been studied in people who have had inflammation of the pancreas (pancreatitis). Trulicity should not be used by people with a history of severe gastrointestinal (GI) disease, people with type 1 diabetes, or people with diabetic ketoacidosis. It is not a substitute for insulin. It has not been studied with long-acting insulin or in children under 18 years of age.

Important Safety Information: Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath while taking Trulicity. These may be symptoms of thyroid cancer. In studies with rats and mice, medicines that work like Trulicity caused thyroid tumors, including thyroid cancer. It is not known if Trulicity will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in people. Do not take Trulicity if you or any of your family members have ever had MTC or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Do not take Trulicity if you have had an allergic reaction to dulaglutide or any of the other ingredients in Trulicity. If you have symptoms of a severe allergic reaction while taking Trulicity, such as itching, rash, or difficulty breathing, stop taking Trulicity and get medical help right away.

If you have pain in your stomach area (abdomen) that is severe and will not go away, stop taking Trulicity and call your healthcare provider right away. The pain may happen with or without vomiting. It may be felt going from your abdomen through to your back. This may be a symptom of inflammation of your pancreas (pancreatitis).

If you are taking another medicine that can cause low blood sugar (such as insulin or a sulfonylurea) while taking Trulicity, your risk for getting low blood sugar (hypoglycemia) may be higher. Talk to your healthcare provider about low blood sugar and how to manage it.

In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration). This may cause kidney problems to get worse.

Other medicines like Trulicity may cause severe stomach problems. It is not known if Trulicity causes or worsens stomach problems.

Tell your healthcare provider if you:

- have or have had problems with your pancreas, kidneys, or liver.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant or plan to become pregnant, or if you become pregnant while taking Trulicity. It is not known if Trulicity will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Trulicity passes into your breast milk. You should not use Trulicity while breastfeeding without first talking to your healthcare provider.

- are taking other medicines including prescription, and over-the-counter medicines, vitamins, and herbal supplements.
- are taking other medicines to treat diabetes, including insulin or sulfonylureas.

The most common side effects with Trulicity may include: nausea, diarrhea, vomiting, decreased appetite, and indigestion. These are not all the possible side effects of Trulicity. Call your doctor for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please click for [Medication Guide](#) and [Full Prescribing Information](#) for Trulicity, including Boxed Warning about possible thyroid tumors including thyroid cancer.

Please see [Instructions for Use](#) included with the pen.

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FDA Approves Albiglutide, a Once-Weekly GLP-1 Injectable Diabetes Drug

The Food and Drug Administration (FDA) has approved albiglutide (*Tanzeum*, GlaxoSmithKline), a once-weekly injectable glucagonlike peptide 1 (GLP-1) receptor agonist to treat type 2 diabetes....

"Tanzeum is a new treatment option for the millions of Americans living with type 2 diabetes," Curtis Rosebraugh, MD, MPH, director of the Office of Drug Evaluation II in the FDA's Center for Drug Evaluation and Research is quoted in a press release. "It can be used alone or added to existing treatment regimens to control blood sugar levels in the overall management of diabetes."

Albiglutide is indicated as monotherapy or in combination therapy with metformin, glimepiride, pioglitazone, or insulin.

Albiglutide, a GLP-1 receptor agonist, is a biological product for the treatment of type 2 diabetes, administered once-weekly using an injector pen supplied with a 5mm 29-gauge thin-walled needle. GLP-1 is an important incretin hormone that helps reduce blood glucose levels but, in people with type 2 diabetes, its production is often reduced or absent.

It is not indicated for patients with type 1 diabetes or diabetic ketoacidosis or as first-line therapy for patients who can't be managed with diet and exercise.

The drug will also carry a boxed warning on its label stating that thyroid C-cell tumors have been observed in rodent studies with some drugs in this class but that it is unknown whether this particular drug causes these types of tumors, including medullary thyroid carcinoma (MTC), in humans.

Albiglutide should not be used in patients who have a personal or family history of MTC or have multiple endocrine neoplasia syndrome type 2 (which predisposes them to MTC).

The FDA is requiring postmarketing studies, including a trial to evaluate dosing, efficacy, and safety in pediatric patients; an MTC case registry of at least 15 years; and a cardiovascular-outcomes trial in patients with high baseline risk of cardiovascular disease.

The most common side effects in clinical trials of albiglutide were diarrhea,

nausea, and injection-site reactions.

The FDA approved albiglutide with a risk evaluation and mitigation strategy (REMS), where the company has a communication plan to inform healthcare providers about the serious risks associated with it.

Albiglutide was approved last month in the European Union under the name *Eperzan*. In the US, it joins other GLP-1 agonists already on the market, including liraglutide (*Victoza*, Novo Nordisk) and exenatide (*Byetta*, AstraZeneca/Bristol-Myers Squibb). Another GLP-1 agonist waiting in the wings is Lilly's dulaglutide.

The FDA approval of albiglutide is based on the results of GSK's comprehensive Phase III Harmony program, consisting of eight trials and involving over 5,000 patients, over 2,000 of whom were treated with Tanzeum. The Harmony studies evaluated albiglutide against commonly-used classes of type 2 diabetes treatment, including insulin, metformin, glimepiride and pioglitazone, in patients at different stages of the disease, as well as those with renal impairment.

Following this approval by the FDA, GSK anticipates the US launch of Tanzeum in the third quarter of 2014.

FDA News Release, 4-15-2014

MEDICATION GUIDE **Rx ONLY**

BYDUREON® (by-DUR-ee-on) (exenatide extended-release for injectable suspension)

Read this Medication Guide and Instructions for Use before you start using BYDUREON (exenatide extended-release for injectable suspension) and each time you get a

There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have questions about BYDUREON after reading this information, ask your healthcare provider or pharmacist.

What is the most important information I should know about BYDUREON?

Serious side effects may happen in people who take BYDUREON, including:

1. Possible thyroid tumors, including cancer. During the drug testing process, the medicine in BYDUREON caused rats to develop tumors of the thyroid gland. Some of these tumors were cancers. It is not known if BYDUREON will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people.

- Before you start taking BYDUREON, tell your healthcare provider if you or any of your family members have had thyroid cancer, especially medullary thyroid cancer, or Multiple Endocrine Neoplasia syndrome type 2. **Do not** take BYDUREON if you or any of your family members have medullary thyroid cancer, or if you have Multiple Endocrine Neoplasia syndrome type 2. People with these conditions already have a higher chance of developing medullary thyroid cancer in general and should not take BYDUREON.
- While taking BYDUREON, tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.

2. Inflammation of the pancreas (pancreatitis), which may be severe and lead to death.

BYDUREON® (exenatide extended-release for injectable suspension)

Before taking BYDUREON, tell your healthcare provider if you have had:

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

These medical conditions can make you more likely to get pancreatitis. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking BYDUREON.

Stop taking BYDUREON and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.

What is BYDUREON?

- BYDUREON is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.
- BYDUREON is a long-acting form of the medication contained in BYETTA. Do not use BYDUREON and BYETTA together.
- BYDUREON is not recommended as the choice of medication for treating diabetes.
- BYDUREON is not insulin.
- It is not known if BYDUREON is safe and effective when used with insulin.
- BYDUREON is not for use in people with type 1 diabetes or people with a condition caused by very high blood sugar (diabetic ketoacidosis).
- It is not known if BYDUREON is safe and effective in children. BYDUREON is not recommended for use in children.
- It is not known if BYDUREON is safe and effective in people who have a history of pancreatitis.
- BYDUREON has not been studied in people who have severe kidney problems.

BYDUREON® (exenatide extended-release for injectable suspension)

Who should not use BYDUREON?

Do not use BYDUREON if:

- you or any of your family members have a history of medullary thyroid cancer.
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body.
- you are allergic to exenatide or any of the ingredients in BYDUREON. See the end of this Medication Guide for a complete list of ingredients in BYDUREON. Symptoms of a severe allergic reaction may include:
 - swelling of your face, lips, tongue, or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - very rapid heartbeat

Talk to your healthcare provider before taking this medicine if you have any of these conditions.

What should I tell my healthcare provider before using BYDUREON?

Before using BYDUREON, tell your healthcare provider if you:

- have any of the conditions listed in the section **“What is the most important information I should know about BYDUREON?”**
- have severe problems with your stomach such as slow emptying of your stomach (gastroparesis) or problems digesting food.
- have or have had kidney problems, or have had a kidney transplant.
- have any other medical conditions.
- are pregnant or are planning to become pregnant. It is not known if BYDUREON may harm your unborn baby. Tell your healthcare provider if you become pregnant while taking BYDUREON.

Pregnancy Registry: A registry has been implemented for women who take BYDUREON during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you take BYDUREON at any time during pregnancy, you

BYDUREON® (exenatide extended-release for injectable suspension)

may enroll in this registry by calling 1-800-633-9081.

- are breastfeeding or plan to breastfeed. It is not known if BYDUREON passes into your breast milk. You and your healthcare provider should decide if you will take BYDUREON or breastfeed. You should not do both without talking with your healthcare provider

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. BYDUREON may affect the way some medicines work and some other medicines may affect the way BYDUREON works.

Especially tell your healthcare provider if you take:

- other diabetes medicines, especially insulin or a sulfonylurea
- any medicine taken by mouth
- warfarin sodium (Coumadin®, Jantoven®)

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use BYDUREON?

For detailed instructions, see the Instructions for Use that comes with your BYDUREON.

- Use BYDUREON exactly as your healthcare provider tells you to.
- BYDUREON is injected once every seven days (weekly) any time during the day.
- BYDUREON is a subcutaneous injection. Inject BYDUREON into your skin exactly the way your healthcare provider told you to. You can take the injection in your stomach area (abdomen), your thigh, or the back of your upper arm. Each week you can use the same area of your body. But be sure to choose a different injection site in that area.
- You can take BYDUREON with or without food.
- **If you miss a dose of BYDUREON, it should be taken as soon as you remember, provided the next regularly scheduled dose is due at least three days later.**

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- **If you miss a dose of BYDUREON and the next regularly scheduled dose is due one or two days later, do not take the missed dose but take BYDUREON on the next regularly scheduled day.**
- **Do not** take 2 doses of BYDUREON less than 3 days apart.
- If you want to change your dosing day, you can. Your new dosing day must be at least 3 days after your last dose.
- Your healthcare provider must teach you how to inject BYDUREON before you use it for the first time. If you have any questions or do not understand the instructions, talk with your healthcare provider or pharmacist.
- BYDUREON must be injected right after you mix it.
- **If you are taking BYETTA and your healthcare provider prescribed BYDUREON, you should follow your healthcare provider's instructions about when to stop taking BYETTA and when to start taking BYDUREON.** BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you change from BYETTA to BYDUREON, your blood sugar levels may be higher than usual and should get better in about 2 weeks.
- Inject your dose of BYDUREON under the skin (subcutaneous injection), as you are told to by your healthcare provider. **Do not inject BYDUREON into a vein or muscle.**
- **Do not** share your BYDUREON tray with another person even if the needle is changed. Sharing your tray with another person can cause you or someone else to get an infection.
- Follow your healthcare provider's instructions for diet, exercise, how often to test your blood sugar, and when to get your HbA_{1c} checked. If you see your blood sugar increasing during treatment with BYDUREON, talk to your healthcare provider because you may need to adjust your current treatment plan for your diabetes.

BYDUREON® (exenatide extended-release for injectable suspension)

- Talk to your healthcare provider about how to manage high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), and how to recognize problems that can happen with your diabetes.

What are the possible side effects of BYDUREON?

BYDUREON can cause serious side effects, including:

- **See “What is the most important information I should know about BYDUREON?”**
- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you take BYDUREON with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while you use BYDUREON. Signs and symptoms of low blood sugar may include:
 - shakiness
 - sweating
 - headache
 - drowsiness
 - weakness
 - dizziness
 - confusion
 - irritability
 - hunger
 - fast heartbeat
 - feeling jittery

Talk with your healthcare provider about how to recognize and treat low blood sugar. Make sure that your family and other people around you a lot know how to recognize and treat low blood sugar.

- **Kidney problems (kidney failure).** BYDUREON may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure, which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration. Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot drink liquids by mouth.
- **Severe allergic reactions.** Severe allergic reactions can happen with BYDUREON. Stop taking BYDUREON,

BYDUREON® (exenatide extended-release for injectable suspension)

and get medical help right away if you have any symptom of a severe allergic reaction. See **“Who should not take BYDUREON?”**

The most common side effects of BYDUREON include:

- nausea
- diarrhea
- headache
- vomiting
- constipation
- itching at the injection site
- a small bump (nodule) at the injection site
- indigestion

Nausea is most common when you start using BYDUREON, but decreases over time in most people as their body gets used to the medicine.

Talk to your healthcare provider about any side effect that bothers you or does not go away.

These are not all the side effects of BYDUREON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BYDUREON?

- Store BYDUREON in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not use BYDUREON past the expiration date. The expiration date is labeled *EXP* and can be found on the paper cover of the single-dose tray.
- Do not freeze BYDUREON trays. Do not use BYDUREON if it has been frozen.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- If needed, you can keep your BYDUREON tray out of the refrigerator at 68°F to 77°F (20°C to 25°C) for up to 4 weeks.
- See the Instructions for Use for information about how to throw away your used BYDUREON parts.

Keep BYDUREON, and all medicines, out of the reach of children.

BYDUREON® (exenatide extended-release for injectable suspension)

General information about safe and effective use of BYDUREON

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BYDUREON for a condition for which it was not prescribed. Do not give your BYDUREON to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about BYDUREON. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BYDUREON that is written for healthcare professionals.

For more information about BYDUREON, go to www.BYDUREON.com or call 1-877-700-7365.

What are the ingredients in BYDUREON?

Contents of vial:

Active Ingredient: exenatide

Inactive Ingredients: polylactide-co-glycolide and sucrose

Contents of liquid (diluent) in syringe:

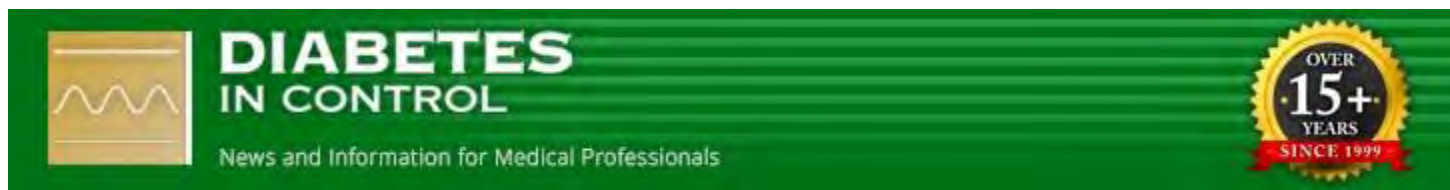
Inactive Ingredients: carboxymethyl-cellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

BYDUREON is a registered trademark and BYETTA is a registered trademark of Amylin Pharmaceuticals, LLC. All other marks are the marks of their respective owners.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850



GLP-1 Agonist Medications Chart

Drug	Generic	Dosing Schedule	Mixing Required	Pre-injection waiting time	Dosing	Smallest Needle Size	Needles included	Approved for use with basal insulin	Auto Injector
Byetta	Exenatide	BID	No	None	5mcg, 10mcg	32 gauge, 4mm needle	No	Yes	No
Bydureon Kit	Exenatide extended release	QW	Yes	None	2mg	23-gauge, 8mm needle	Yes	No Currently studies are evaluating	No
Bydureon Pen	Exenatide extended release	QW	Yes	None	2mg	23-gauge, 7mm needle	Yes	No Currently studies are evaluating	No
Tanzeum	Albiglutide	QW	Yes	Yes 15-30 minutes	30mg, 50mg	29-gauge, 5mm needle	Yes	Yes	No
Trulicity	Dulaglutide	QW	No	None	0.75mg, 1.5mg	Built in to device 29 gauge, 5mm needle	Yes part of device	No Currently studies are evaluating	Yes
Victoza	Liraglutide	QD	No	None	0.6, 1.2, 1.8mg	32 gauge, 4mm needle	No	Yes	No

Package Insert (PI) list

Byetta (exenatide) AZ - http://www.azpicentral.com/byetta/pi_byetta.pdf#page=1

Bydureon Pen and Kit (exenatide extended release) AZ -

http://www.azpicentral.com/bydureon/pi_bydureon.pdf#page=1

Tanzeum (albiglutide) GSK - <http://www.gsksource.com/gskprm/htdocs/documents/TANZEUM-PI-MG-IFU-COMBINED.PDF>

Trulicity (dulaglutide) LILLY - <http://pi.lilly.com/us/trulicity-uspi.pdf>

Victoza (liraglutide) NOVO - <http://www.novo-pi.com/victoza.pdf>

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TANZEUM safely and effectively. See full prescribing information for TANZEUM.

TANZEUM (albiglutide) for injection, for subcutaneous use
Initial U.S. Approval: 2014

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether TANZEUM causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. (5.1)
- TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). (4.1, 5.1)

INDICATIONS AND USAGE

TANZEUM is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. (1, 5.1)
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. (1, 5.2)
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- Not for patients with pre-existing severe gastrointestinal disease. (1)
- Has not been studied in combination with prandial insulin. (1)

DOSAGE AND ADMINISTRATION

- Administer once weekly at any time of day, without regard to meals. (2.1)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.1)
- Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control. (2.1)
- If a dose is missed, administer within 3 days of missed dose. (2.1)
- See Full Prescribing Information and Patient Instructions for Use for reconstitution of lyophilized powder and administration. (2.4, 2.5, 17)

DOSAGE FORMS AND STRENGTHS

For injection: 30 mg or 50 mg in a single-dose Pen. (3)

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2. (4.1)
- History of serious hypersensitivity to albiglutide or any product components. (4.2, 5.4)

WARNINGS AND PRECAUTIONS

- Pancreatitis: Discontinue promptly if suspected. Do not restart if confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis. (5.2)
- Hypoglycemia: Can occur when used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Consider lowering sulfonylurea or insulin dosage when starting TANZEUM. (5.3)
- Hypersensitivity Reactions: Discontinue TANZEUM if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve. (5.4)
- Renal Impairment: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- Macrovascular Outcomes: There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with TANZEUM or any other antidiabetic drug. (5.6)

ADVERSE REACTIONS

Adverse reactions, reported in $\geq 10\%$ of patients treated with TANZEUM and more frequently than in patients on placebo, were upper respiratory tract infection, diarrhea, nausea, and injection site reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

TANZEUM delays gastric emptying. May impact absorption of concomitantly administered oral medications. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: TANZEUM may cause fetal harm; only use if potential benefit justifies potential risk to fetus. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue TANZEUM. (8.3)
- Renal Impairment: No dosage adjustment recommended. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2014

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether TANZEUM™ causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans [see Warnings and Precautions (5.1)].**
- **TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with TANZEUM. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see Contraindications (4.1), Warnings and Precautions (5.1)].**

1 INDICATIONS AND USAGE

TANZEUM is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see Clinical Studies (14)].

Limitations of Use:

- TANZEUM is not recommended as first-line therapy for patients inadequately controlled on diet and exercise [see Warnings and Precautions (5.1)].
- TANZEUM has not been studied in patients with a history of pancreatitis [see Warnings and Precautions (5.2)]. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- TANZEUM is not indicated in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. TANZEUM is not a substitute for insulin in these patients.
- TANZEUM has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of TANZEUM is not recommended in patients with pre-existing severe gastrointestinal disease [see Adverse Reactions (6.1)].
- TANZEUM has not been studied in combination with prandial insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dosage of TANZEUM is 30 mg once weekly given as a subcutaneous injection in the abdomen, thigh, or upper arm region. The dosage may be increased to 50 mg once weekly if the glycemic response is inadequate.

TANZEUM may be administered at any time of day without regard to meals. Instruct patients to administer TANZEUM once a week on the same day each week. The day of weekly administration may be changed if necessary as long as the last dose was administered 4 or more days before.

If a dose is missed, instruct patients to administer as soon as possible within 3 days after the missed dose. Thereafter, patients can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, instruct patients to wait until their next regularly scheduled weekly dose.

2.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating TANZEUM, consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia [*see Warnings and Precautions (5.3)*].

2.3 Dosage in Patients with Renal Impairment

No dose adjustment is needed in patients with mild, moderate, or severe renal impairment (eGFR 15 to 89 mL/min/1.73 m²). Use caution when initiating or escalating doses of TANZEUM in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions [*see Warnings and Precautions (5.5), Use in Specific Populations (8.6)*].

2.4 Reconstitution of the Lyophilized Powder

The lyophilized powder contained within the Pen must be reconstituted prior to administration. See Patient Instructions for Use for complete administration instructions with illustrations. The instructions may also be found at www.TANZEUM.com. Instruct patients as follows:

Pen Reconstitution

- a) Hold the Pen body with the clear cartridge pointing up to see the [1] in the number window.
- b) To reconstitute the lyophilized powder with the diluent in the Pen, twist the clear cartridge on the Pen in the direction of the arrow until the Pen is felt/heard to “click” into place and the [2] is seen in the number window. This mixes the diluent with the lyophilized powder.
- c) Slowly and gently rock the Pen side-to-side 5 times to mix the reconstituted solution of TANZEUM. Advise the patient to not shake the Pen hard to avoid foaming.
- d) Wait 15 minutes for the 30-mg Pen and 30 minutes for the 50-mg Pen to ensure that the reconstituted solution is mixed.

Preparing Pen for Injection

- e) Slowly and gently rock the Pen side-to-side 5 additional times to mix the reconstituted solution.
- f) Visually inspect the reconstituted solution in the viewing window for particulate matter. The reconstituted solution will be yellow in color. After reconstitution, use TANZEUM within 8 hours.
- g) Holding the Pen upright, attach the needle to the Pen. Gently tap the clear cartridge to bring large bubbles to the top.

See *Dosage and Administration (2.5)* for important administration instructions, including the injection procedure.

Alternate Method of Reconstitution (Healthcare Professional Use Only)

The Patient Instructions for Use provide directions for the patient to wait 15 minutes for the 30-mg Pen and 30 minutes for the 50-mg Pen after the lyophilized powder and diluent are mixed to ensure reconstitution.

Healthcare professionals may utilize the following alternate method of reconstitution. Because this method relies on appropriate swirling and visual inspection of the solution, it should only be performed by healthcare professionals.

- a) Follow Step A (Inspect Your Pen and Mix Your Medication) in the Instructions for Use. Make sure you have:
 - Inspected the Pen for [1] in the number window and expiration date.
 - Twisted the clear cartridge until [2] appears in the number window and a “click” is heard. This combines the medicine powder and liquid in the clear cartridge.
- b) Hold the Pen with the clear cartridge pointing up and maintain this orientation throughout the reconstitution.
- c) Gently swirl the Pen in small circular motions for at least one minute. Avoid shaking as this can result in foaming, which may affect the dose.
- d) Inspect the solution, and if needed, continue to gently swirl the Pen until all the powder is dissolved and you see a clear yellow solution that is free of particles. A small amount of foam, on top of the solution at the end of reconstitution, is normal.
 - For 30-mg Pen: Complete dissolution usually occurs within 2 minutes but may take up to 5 minutes, as confirmed by visual inspection for a clear yellow solution free of particles.
 - For 50-mg Pen: Complete dissolution usually occurs within 7 minutes but may take up to 10 minutes.
- e) After reconstitution, continue to follow the steps in the Instructions for Use, starting at Step B: Attach the Needle.

2.5 Important Administration Instructions

Instruct patients as follows:

- The pen should be used within 8 hours of reconstitution prior to attaching the needle.
- After attaching the supplied needle, remove air bubbles by slowly twisting the Pen until you see the [3] in the number window. At the same time, the injection button will be automatically released from the bottom of the Pen.
- Use immediately after the needle is attached and primed. The product can clog the needle if allowed to dry in the primed needle.

- After subcutaneously inserting the needle into the skin in the abdomen, thigh, or upper arm region, press the injection button. Hold the injection button until you hear a “click” and then hold the button for 5 additional seconds to deliver the full dose.

When using TANZEUM with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject TANZEUM and insulin in the same body region but the injections should not be adjacent to each other.

When injecting in the same body region, advise patients to use a different injection site each week. TANZEUM must not be administered intravenously or intramuscularly.

3 DOSAGE FORMS AND STRENGTHS

TANZEUM is supplied as follows:

- For injection: 30-mg lyophilized powder in a single-dose Pen (pen injector) for reconstitution.
- For injection: 50-mg lyophilized powder in a single-dose Pen (pen injector) for reconstitution.

4 CONTRAINDICATIONS

4.1 Medullary Thyroid Carcinoma

TANZEUM is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see *Warnings and Precautions (5.1)*].

4.2 Hypersensitivity

TANZEUM is contraindicated in patients with a prior serious hypersensitivity reaction to albiglutide or to any of the product components [see *Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Nonclinical studies in rodents of clinically relevant doses of GLP-1 receptor agonists showed dose-related and treatment-duration-dependent increases in the incidence of thyroid C-cell tumors (adenomas and carcinomas). Carcinogenicity studies could not be conducted with TANZEUM because drug-clearing, anti-drug antibodies develop in animals used for these types of studies [see *Nonclinical Toxicology (13.1)*]. It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors, including MTC in humans [see *Boxed Warning, Contraindications (4.1)*].

Across 8 Phase III clinical trials [see *Clinical Studies (14)*], MTC was diagnosed in 1 patient receiving TANZEUM and 1 patient receiving placebo. Both patients had markedly elevated serum calcitonin levels at baseline.

TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the risk for MTC with the use of TANZEUM and

inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). The clinical value of routine monitoring of serum calcitonin to diagnose MTC in patients at risk for MTC has not been established.

Elevated serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with TANZEUM. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

5.2 Acute Pancreatitis

In clinical trials, acute pancreatitis has been reported in association with TANZEUM.

Across 8 Phase III clinical trials [*see Clinical Studies (14)*], pancreatitis adjudicated as likely related to therapy occurred more frequently in patients receiving TANZEUM (6 of 2,365 [0.3%]) than in patients receiving placebo (0 of 468 [0%]) or active comparators (2 of 2,065 [0.1%]).

After initiation of TANZEUM, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue TANZEUM. If pancreatitis is confirmed, TANZEUM should not be restarted.

TANZEUM has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

The risk of hypoglycemia is increased when TANZEUM is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Therefore, patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia in this setting [*see Adverse Reactions (6.1)*].

5.4 Hypersensitivity Reactions

Across 8 Phase III clinical trials [*see Clinical Studies (14)*], a serious hypersensitivity reaction with pruritus, rash, and dyspnea occurred in a patient treated with TANZEUM. If hypersensitivity reactions occur, discontinue use of TANZEUM; treat promptly per standard of care and monitor until signs and symptoms resolve [*see Contraindications (4.2)*].

5.5 Renal Impairment

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In a trial of TANZEUM in patients with renal impairment [*see Clinical Studies*

(14.3)], the frequency of such gastrointestinal reactions increased as renal function declined [see *Use in Specific Populations* (8.6)]. Because these reactions may worsen renal function, use caution when initiating or escalating doses of TANZEUM in patients with renal impairment [see *Dosage and Administration* (2.3), *Use in Specific Populations* (8.6)].

5.6 Macrovascular Outcomes

There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with TANZEUM or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious reactions are described below or elsewhere in the labeling:

- Risk of Thyroid C-cell Tumors [see *Warnings and Precautions* (5.1)]
- Acute Pancreatitis [see *Warnings and Precautions* (5.2)]
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin [see *Warnings and Precautions* (5.3)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.4)]
- Renal Impairment [see *Warnings and Precautions* (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from 4 placebo-controlled trials. TANZEUM was used as monotherapy in 1 trial and as add-on therapy in 3 trials [see *Clinical Studies* (14)]. These data reflect exposure of 923 patients to TANZEUM and a mean duration of exposure to TANZEUM of 93 weeks. The mean age of participants was 55 years, 1% of participants were 75 years or older and 53% of participants were male. The population in these studies was 48% white, 13% African/African American, 7% Asian, and 29% Hispanic/Latino. At baseline, the population had diabetes for an average of 7 years and had a mean HbA1c of 8.1%. At baseline, 17% of the population in these studies reported peripheral neuropathy and 4% reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR >60 mL/min/1.73 m²) in 91% of the study population and moderately impaired (eGFR 30 to 60 mL/min/1.73 m²) in 9%.

Table 1 shows common adverse reactions excluding hypoglycemia associated with the use of TANZEUM in the pool of placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on TANZEUM than on placebo, and occurred in at least 5% of patients treated with TANZEUM.

Table 1. Adverse Reactions in Placebo-controlled Trials Reported in $\geq 5\%$ of Patients Treated with TANZEUM^a

Adverse Reaction	Placebo (N = 468) %	TANZEUM (N = 923) %
Upper respiratory tract infection	13.0	14.2
Diarrhea	10.5	13.1
Nausea	9.6	11.1
Injection site reaction ^b	2.1	10.5
Cough	6.2	6.9
Back pain	5.8	6.7
Arthralgia	6.4	6.6
Sinusitis	5.8	6.2
Influenza	3.2	5.2

^a Adverse reactions reported includes adverse reactions occurring with the use of glycemic rescue medications which included metformin (17% for placebo and 10% for TANZEUM) and insulin (24% for placebo and 14% for TANZEUM).

^b See below for other events of injection site reactions reported.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal complaints occurred more frequently among patients receiving TANZEUM (39%) than patients receiving placebo (33%). In addition to diarrhea and nausea (see Table 1), the following gastrointestinal adverse reactions also occurred more frequently in patients receiving TANZEUM: vomiting (2.6% versus 4.2% for placebo versus TANZEUM), gastroesophageal reflux disease (1.9% versus 3.5% for placebo versus TANZEUM), and dyspepsia (2.8% versus 3.4% for placebo versus TANZEUM). Constipation also contributed to the frequently reported reactions. In the group treated with TANZEUM, investigators graded the severity of GI reactions as “mild” in 56% of cases, “moderate” in 37% of cases, and “severe” in 7% of cases. Discontinuation due to GI adverse reactions occurred in 2% of individuals on TANZEUM or placebo.

Injection Site Reactions

In the pool of placebo-controlled trials, injection site reactions occurred more frequently on TANZEUM (18%) than on placebo (8%). In addition to the term injection site reaction (see Table 1), the following other types of injection site reactions also occurred more frequently on TANZEUM: injection site hematoma (1.9% versus 2.1% for placebo versus TANZEUM), injection site erythema (0.4% versus, 1.7% for placebo versus TANZEUM), injection site rash (0% versus 1.4% for placebo versus TANZEUM), injection site hypersensitivity (0% versus 0.8% for placebo versus TANZEUM), and injection site hemorrhage (0.6% versus 0.7% for placebo versus TANZEUM). Injection site pruritus also contributed to the frequently reported reactions. The majority of injection site reactions were judged as “mild” by investigators in both groups (73% for TANZEUM versus 94% for placebo). More patients on TANZEUM than on placebo: discontinued due to an injection site reaction (2% versus 0.2%), experienced more than 2 reactions (38% versus 20%), had a reaction judged by investigators to be “moderate” or

“severe” (27% versus 6%) and required local or systemic treatment for the reactions (36% versus 11%).

Pool of Placebo- and Active-controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 7 placebo- and active-controlled trials. These trials evaluated the use of TANZEUM as monotherapy, and as add-on therapy to oral antidiabetic agents, and as add-on therapy to basal insulin [see *Clinical Studies (14)*]. In this pool, a total of 2,116 patients with type 2 diabetes were treated with TANZEUM for a mean duration of 75 weeks. The mean age of patients treated with TANZEUM was 55 years, 1.5% of the population in these studies was 75 years or older and 51% of participants were male. Forty-eight percent of patients were white, 15% African/African American, 9% Asian, and 26% were Hispanic/Latino. At baseline, the population had diabetes for an average of 8 years and had a mean HbA1c of 8.2%. At baseline, 21% of the population reported peripheral neuropathy and 5% reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR >60 mL/min/1.73 m²) in 92% of the population and moderately impaired (eGFR 30 to 60 mL/min/1.73 m²) in 8% of the population.

In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions excluding hypoglycemia were similar to those listed in Table 1.

Other Adverse Reactions

Hypoglycemia

The proportion of patients experiencing at least one documented symptomatic hypoglycemic episode on TANZEUM and the proportion of patients experiencing at least one severe hypoglycemic episode on TANZEUM in clinical trials [see *Clinical Studies (14)*] is shown in Table 2. Hypoglycemia was more frequent when TANZEUM was added to sulfonylurea or insulin [see *Warnings and Precautions (5.3)*].

Table 2. Incidence (%) of Hypoglycemia in Clinical Trials of TANZEUM^a

Monotherapy^b (52 Weeks)	Placebo N = 101	TANZEUM 30 mg Weekly N = 101
Documented symptomatic ^c	2%	2%
Severe ^d	-	-
In Combination with Metformin Trial (104 Weeks)^e	Placebo N = 101	TANZEUM N = 302
Documented symptomatic	4%	3%
Severe	-	-
In Combination with Pioglitazone ± Metformin (52 Weeks)	Placebo N = 151	TANZEUM N = 150
Documented symptomatic	1%	3%
Severe	-	1%
In Combination with Metformin and Sulfonylurea (52 Weeks)	Placebo N = 115	TANZEUM N = 271
Documented symptomatic	7%	13%
Severe	-	0.4%
In Combination with Insulin Glargine (26 Weeks)	Insulin Lispro N = 281	TANZEUM N = 285
Documented symptomatic	30%	16%
Severe	0.7%	-
In Combination with Metformin ± Sulfonylurea (52 Weeks)	Insulin Glargine N = 241	TANZEUM N = 504
Documented symptomatic	27%	17%
Severe	0.4%	0.4%
In Combination with OADs in Renal Impairment (26 Weeks)	Sitagliptin N = 246	TANZEUM N = 249
Documented symptomatic	6%	10%
Severe	0.8%	-

OAD = Oral antidiabetic agents.

^a Data presented are to the primary endpoint and include only events occurring on-therapy with randomized medications and excludes events occurring after use of glycemic rescue medications (i.e., primarily metformin or insulin).

^b In this trial, no documented symptomatic or severe hypoglycemia were reported for TANZEUM 50 mg and these data are omitted from the table.

^c Plasma glucose concentration ≤ 70 mg/dL and presence of hypoglycemic symptoms.

^d Event requiring another person to administer a resuscitative action.

^e Rate of documented symptomatic hypoglycemia for active controls 18% (glimepiride) and 2% (sitagliptin).

Pneumonia

In the pool of 7 placebo- and active-controlled trials, the adverse reaction of pneumonia was reported more frequently in patients receiving TANZEUM (1.8%) than in patients in the all-comparators group (0.8%). More cases of pneumonia in the group receiving TANZEUM were serious (0.4% for TANZEUM versus 0.1% for all comparators).

Atrial Fibrillation/Flutter

In the pool of 7 placebo- and active-controlled trials, adverse reactions of atrial fibrillation (1.0%) and atrial flutter (0.2%) were reported more frequently for TANZEUM than for all comparators (0.5% and 0%, respectively). In both groups, patients with events were generally male, older, and had underlying renal impairment or cardiac disease (e.g., history of arrhythmia, palpitations, congestive heart failure, cardiomyopathy, etc.).

Appendicitis

In the pool of placebo- and active-controlled trials, serious events of appendicitis occurred in 0.3% of patients treated with TANZEUM compared with 0% among all comparators.

Immunogenicity

In the pool of 7 placebo- and active-controlled trials, 116 (5.5%) of 2,098 patients exposed to TANZEUM tested positive for anti-albiglutide antibodies at any time during the trials. None of these antibodies were shown to neutralize the activity of albiglutide in an in vitro bioassay. Presence of antibody did not correlate with reduced efficacy as measured by HbA1c and fasting plasma glucose or specific adverse reactions.

Consistent with the high homology of albiglutide with human GLP-1, the majority of patients (approximately 79%) with anti-albiglutide antibodies also tested positive for anti-GLP-1 antibodies; none were neutralizing. A minority of patients (approximately 17%) who tested positive for anti-albiglutide antibodies also transiently tested positive for antibodies to human albumin.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to albiglutide cannot be directly compared with the incidence of antibodies of other products.

Liver Enzyme Abnormalities

In the pool of placebo- and active-controlled trials, a similar proportion of patients experienced at least one event of alanine aminotransferase (ALT) increase of 3-fold or greater above the upper limit of normal (0.9% and 0.9% for all comparators versus TANZEUM). Three subjects on TANZEUM and one subject in the all-comparator group experienced at least one event of ALT increase of 10-fold or greater above the upper limit of normal. In one of the 3 cases an alternate etiology was identified to explain the rise in liver enzyme (acute viral hepatitis). In one case, insufficient information was obtained to establish or refute a drug-related causality. In the third

case, elevation in ALT (10 times the upper limit of normal) was accompanied by an increase in total bilirubin (4 times the upper limit of normal) and occurred 8 days after the first dose of TANZEUM. The etiology of hepatocellular injury was possibly related to TANZEUM but direct attribution to TANZEUM was confounded by the presence of gallstone disease diagnosed on ultrasound 3 weeks after the event.

Gamma Glutamyltransferase (GGT) Increase

In the pool of placebo-controlled trials, the adverse event of increased GGT occurred more frequently in the group treated with TANZEUM (0.9% and 1.5% for placebo versus TANZEUM).

Heart Rate Increase

In the pool of placebo-controlled trials, mean heart rate in patients treated with TANZEUM was higher by an average of 1 to 2 bpm compared with mean heart rate in patients treated with placebo across study visits. The long-term clinical effects of the increase in heart rate have not been established [see *Warnings and Precautions* (5.6)].

7 DRUG INTERACTIONS

TANZEUM did not affect the absorption of orally administered medications tested in clinical pharmacology studies to any clinically relevant degree [see *Clinical Pharmacology* (12.3)]. However, TANZEUM causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with TANZEUM.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of TANZEUM in pregnant women. Nonclinical studies have shown reproductive toxicity, but not teratogenicity, in mice treated with albiglutide at up to 39 times human exposure resulting from the maximum recommended dose of 50 mg/week, based on AUC [see *Nonclinical Toxicology* (13.1, 13.3)]. TANZEUM should not be used during pregnancy unless the expected benefit outweighs the potential risks.

Due to the long washout period for TANZEUM, consider stopping TANZEUM at least 1 month before a planned pregnancy.

There are no data on the effects of TANZEUM on human fertility. Studies in mice showed no effects on fertility [see *Nonclinical Toxicology* (13.1)]. The potential risk to human fertility is unknown.

8.3 Nursing Mothers

There are no adequate data to support the use of TANZEUM during lactation in humans.

It is not known if TANZEUM is excreted into human milk during lactation. Given that TANZEUM is an albumin-based protein therapeutic, it is likely to be present in human milk.

Decreased body weight in offspring was observed in mice treated with TANZEUM during gestation and lactation [see *Nonclinical Toxicology* (13.3)]. A decision should be made whether to discontinue nursing or to discontinue TANZEUM, taking into account the importance of the drug to the mother and the potential risks to the infant.

8.4 Pediatric Use

Safety and effectiveness of TANZEUM have not been established in pediatric patients (younger than 18 years).

8.5 Geriatric Use

Of the total number of patients (N = 2,365) in 8 Phase III clinical trials who received TANZEUM, 19% (N = 444) were 65 years and older, and <3% (N = 52) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Of the total number of patients (N = 2,365) in 8 Phase III clinical trials who received TANZEUM, 54% (N = 1,267) had mild renal impairment (eGFR 60 to 89 mL/min/1.73 m²), 12% (N = 275) had moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m²) and 1% (N = 19) had severe renal impairment (eGFR 15 to <30 mL/min/1.73 m²).

No dosage adjustment is required in patients with mild (eGFR 60 to 89 mL/min/1.73 m²), moderate (eGFR 30 to 59 mL/min/1.73 m²), or severe (eGFR 15 to <30 mL/min/1.73 m²) renal impairment.

Efficacy of TANZEUM in patients with type 2 diabetes and renal impairment is described elsewhere [see *Clinical Studies* (14.3)]. There is limited clinical experience in patients with severe renal impairment (19 subjects). The frequency of GI events increased as renal function declined. For patients with mild, moderate, or severe impairment, the respective event rates were: diarrhea (6%, 13%, 21%), nausea (3%, 5%, 16%), and vomiting (1%, 2%, 5%). Therefore, caution is recommended when initiating or escalating doses of TANZEUM in patients with renal impairment [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.5), *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

No data are available with regard to overdosage in humans. Anticipated symptoms of an overdose may be severe nausea and vomiting.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of TANZEUM (5 days).

11 DESCRIPTION

TANZEUM is a GLP-1 receptor agonist, a recombinant fusion protein comprised of 2 tandem copies of modified human GLP-1 genetically fused in tandem to human albumin. The human GLP-1 fragment sequence 7 – 36 has been modified with a glycine substituted for the naturally-

occurring alanine at position 8 in order to confer resistance to dipeptidylpeptidase IV (DPP-IV) mediated proteolysis. The human albumin moiety of the recombinant fusion protein, together with the DPP-IV resistance, extends the half-life allowing once-weekly dosing. TANZEUM has a molecular weight of 72,970 Daltons.

TANZEUM is produced by a strain of *Saccharomyces cerevisiae* modified to express the therapeutic protein.

TANZEUM 30-mg Pen for injection (for subcutaneous use) contains 40.3 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 30 mg in a volume of 0.5 mL after reconstitution.

TANZEUM 50-mg Pen for injection (for subcutaneous use) contains 67 mg lyophilized albiglutide and 0.65 mL Water for Injection diluent designed to deliver a dose of 50 mg in a volume of 0.5 mL after reconstitution.

The lyophilized powder of both dose strengths is white to yellow in color and the solvent is a clear and colorless solution. The reconstituted solution is yellow in color.

Inactive ingredients include 153 mM mannitol, 0.01% (w/w) polysorbate 80, 10 mM sodium phosphate, and 117 mM trehalose dihydrate. TANZEUM does not contain a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TANZEUM is an agonist of the GLP-1 receptor and augments glucose-dependent insulin secretion. TANZEUM also slows gastric emptying.

12.2 Pharmacodynamics

TANZEUM lowers fasting glucose and reduces postprandial glucose excursions in patients with type 2 diabetes mellitus. The majority of the observed reduction in fasting plasma glucose occurs after a single dose, consistent with the pharmacokinetic profile of albiglutide. In a Phase II trial in Japanese patients with type 2 diabetes mellitus who received TANZEUM 30 mg, a reduction (22%) in postprandial glucose AUC_(0-3 h) was observed at steady state (Week 16) compared with placebo following a mixed meal.

A single dose of TANZEUM 50 mg subcutaneous (SC) did not impair glucagon response to low glucose concentrations.

Gastric Motility

TANZEUM slowed gastric emptying compared with placebo for both solids and liquids when albiglutide 100 mg (2 times the maximum approved dosage) was administered as a single dose in healthy subjects.

Cardiac Electrophysiology

At doses up to the maximum recommended dose (50 mg), TANZEUM does not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following SC administration of a single 30-mg dose to subjects with type 2 diabetes mellitus, maximum concentrations of albiglutide were reached at 3 to 5 days post-dosing. The mean peak concentration (C_{max}) and mean area under the time-concentration curve (AUC) of albiglutide were 1.74 mcg/mL and 465 mcg.h/mL, respectively, following a single dose of 30 mg albiglutide in type 2 diabetes mellitus subjects. Steady-state exposures are achieved following 4 to 5 weeks of once-weekly administration. Exposures at the 30-mg and 50-mg dose levels were consistent with a dose-proportional increase. Similar exposure is achieved with SC administration of albiglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of albiglutide following SC administration has not been evaluated.

Distribution

The mean estimate of apparent volume of distribution of albiglutide following SC administration is 11 L. As albiglutide is an albumin fusion molecule, plasma protein binding has not been assessed.

Metabolism

Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed. Because albiglutide is an albumin fusion protein, it likely follows a metabolic pathway similar to native human serum albumin which is catabolized primarily in the vascular endothelium.

Elimination

The mean apparent clearance of albiglutide is 67 mL/h with an elimination half-life of approximately 5 days, making albiglutide suitable for once-weekly administration.

Specific Patient Populations

Age, Gender, Race, and Body Weight: Based on the population pharmacokinetic analysis with data collected from 1,113 subjects, age, gender, race, and body weight had no clinically relevant effect on the pharmacokinetics of albiglutide.

Pediatric: No pharmacokinetic data are available in pediatric patients.

Renal: In a population pharmacokinetic analysis including a Phase III trial in patients with mild, moderate, and severe renal impairment, exposures were increased by approximately 30% to 40% in severe renal impairment compared with those observed in type 2 diabetic patients with normal renal function.

Hepatic: No clinical trials were conducted to examine the effects of mild, moderate, or severe hepatic impairment on the pharmacokinetics of albiglutide. Therapeutic proteins such as albiglutide are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide.

Drug Interactions

In multiple-dose, drug-drug interaction trials no significant change in systemic exposures of the co-administered drugs were observed, except simvastatin (see Table 3). When albiglutide was co-administered with simvastatin, $C_{\max}$ of simvastatin and its active metabolite simvastatin acid was increased by approximately 18% and 98%, respectively. In the same trial, AUC of simvastatin decreased by 40% and AUC of simvastatin acid increased by 36%. Clinical relevance of these changes has not been established (see Table 3).

Additionally, no clinically relevant pharmacodynamic effects on luteinizing hormone, follicle-stimulating hormone, or progesterone were observed when albiglutide and a combination oral contraceptive were co-administered. Albiglutide did not significantly alter the pharmacodynamic effects of warfarin as measured by the international normalized ratio (INR).

Table 3. Effect of Albiglutide on Systemic Exposure of Co-administered Drugs

Co-administered Drug	Dose of Co-administered Drug ^a	Dose of TANZEUM	Geometric Mean Ratio (Ratio +/- Co-administered Drug) No Effect = 1		
			Analyte	AUC (90% CI) ^b	C _{max} (90% CI)
			No dose adjustments of co-administered drug required for the following:		
Simvastatin	80 mg	50 mg QW for 5 weeks	Simvastatin	0.60 (0.52 – 0.69)	1.18 (1.02 – 1.38)
			Simvastatin acid	1.36 (1.19 – 1.55)	1.98 (1.75 – 2.25)
Digoxin	0.5 mg	50 mg QW for 5 weeks	Digoxin	1.09 (1.01 – 1.18)	1.11 (0.98 – 1.26)
Oral contraceptive ^c	0.035 mg ethinyl estradiol and 0.5 mg norethindrone	50 mg QW for 4 weeks	Norethindrone	1.00 (0.96 – 1.04)	1.04 (0.98 – 1.10)
			Levonorgestrel	1.09 (1.06 – 1.14)	1.20 (1.11 – 1.29)
Warfarin	25 mg	50 mg QW for 5 weeks	R-Warfarin	1.02 (0.98 – 1.07)	0.94 (0.89 – 0.99)
			S-Warfarin	0.99 (0.95 – 1.03)	0.93 (0.87 – 0.98)

QW = Once weekly.

^a Single dose unless otherwise noted.

^b AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses.

^c Subjects received low-dose oral contraceptive for two 28-day treatment cycles (21 days active/7 days placebo).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

As albiglutide is a recombinant protein, no genotoxicity studies have been conducted.

Carcinogenicity studies have not been performed with albiglutide because such studies are not technically feasible due to the rapid development of drug-clearing, anti-drug antibodies in rodents. Thyroid C-cell tumors were observed in 2-year rodent carcinogenicity studies with some GLP-1 receptor agonists. The clinical relevance of rodent thyroid findings observed with GLP-1 receptor agonists is unknown.

In a mouse fertility study, males were treated with SC doses of 5, 15, or 50 mg/kg/day for 7 days prior to cohabitation with females, and continuing through mating. In a separate fertility study, females were treated with SC doses of 1, 5, or 50 mg/kg/day for 7 days prior to cohabitation with males, and continuing through mating. Reductions in estrous cycles were observed at 50 mg/kg/day, a dose associated with maternal toxicity (body weight loss and reduced food consumption). There were no effects on mating or fertility in either sex at doses up to 50 mg/kg/day (up to 39 times clinical exposure based on AUC).

13.3 Reproductive and Developmental Toxicity

In order to minimize the impact of the drug-clearing, anti-drug antibody response, reproductive and developmental toxicity assessments in the mouse were partitioned to limit the dosing period to no more than approximately 15 days in each study.

In pregnant mice given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 1 to 6, there were no adverse effects on early embryonic development through implantation at 50 mg/kg/day (39 times clinical exposure based on AUC).

In pregnant mice given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 6 through 15 (organogenesis), embryo-fetal lethality (post-implantation loss) and bent (wavy) ribs were observed at 50 mg/kg/day (39 times clinical exposure based on AUC), a dose associated with maternal toxicity (body weight loss and reduced food consumption).

Pregnant mice were given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 6 to 17. Offspring of pregnant mice given 50 mg/kg/day (39 times clinical exposure based on AUC), a dose associated with maternal toxicity, had reduced body weight pre-weaning, dehydration and coldness, and a delay in balanopreputial separation.

Pregnant mice were given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 15 to lactation Day 10. Increased mortality and morbidity were seen at all doses (≥ 1 mg/kg/day) in lactating females in mouse pre- and postnatal development studies. Mortalities have not been observed in previous toxicology studies in non-lactating or non-pregnant mice, nor in pregnant mice. These findings are consistent with lactational ileus syndrome which has been previously reported in mice. Since the relative stress of lactation energy demands is lower in humans than mice and humans have large energy reserves, the mortalities observed in lactating mice are of questionable relevance to humans. The offspring had decreased pre-weaning body weight which reversed post-weaning in males but not females at ≥ 5 mg/kg/day (2.2 times clinical exposure based on AUC) with no other effects on development. Low levels of albiglutide were detected in plasma of offspring.

Lactating mice were given SC doses of 1, 5, or 50 mg/kg/day from lactation Day 7 to 21 (weaning) under conditions that limit the impact of lactational ileus (increased caloric intake and

culling of litters). Doses ≥ 1 mg/kg/day (exposures below clinical AUC) caused reduced weight gain in the pups during the treatment period.

14 CLINICAL STUDIES

TANZEUM has been studied as monotherapy and in combination with metformin, metformin and a sulfonylurea, a thiazolidinedione (with and without metformin), and insulin glargine (with or without oral anti-diabetic drugs). The efficacy of TANZEUM was compared with placebo, glimepiride, pioglitazone, liraglutide, sitagliptin, insulin lispro, and insulin glargine.

Trials evaluated the use of TANZEUM 30 mg and 50 mg. Five of the 8 trials allowed optional uptitration of TANZEUM from 30 mg to 50 mg if glycemic response with 30 mg was inadequate.

In patients with type 2 diabetes mellitus, TANZEUM produced clinically relevant reduction from baseline in HbA1c compared with placebo. No overall differences in glycemic effectiveness or body weight were observed across demographic subgroups (age, gender, race/ethnicity, duration of diabetes).

14.1 Monotherapy

The efficacy of TANZEUM as monotherapy was evaluated in a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. In this trial, 296 patients with type 2 diabetes inadequately controlled on diet and exercise were randomized (1:1:1) to TANZEUM 30 mg SC once weekly, TANZEUM 30 mg SC once weekly uptitrated to 50 mg once weekly at Week 12, or placebo. The mean age of participants was 53 years, 55% of patients were men, the mean duration of diabetes was 4 years, and the mean baseline eGFR was 84 mL/min/1.73 m². Primary and secondary efficacy results are presented in Table 4. Figure 1 shows the mean adjusted changes in HbA1c from baseline across study visits.

Compared with placebo, treatment with TANZEUM 30 mg or 50 mg resulted in statistically significant reductions in HbA1c from baseline at Week 52 (see Table 4). The adjusted mean change in weight from baseline did not differ significantly between TANZEUM (-0.4 to -0.9 kg) and placebo (-0.7 kg) at Week 52.

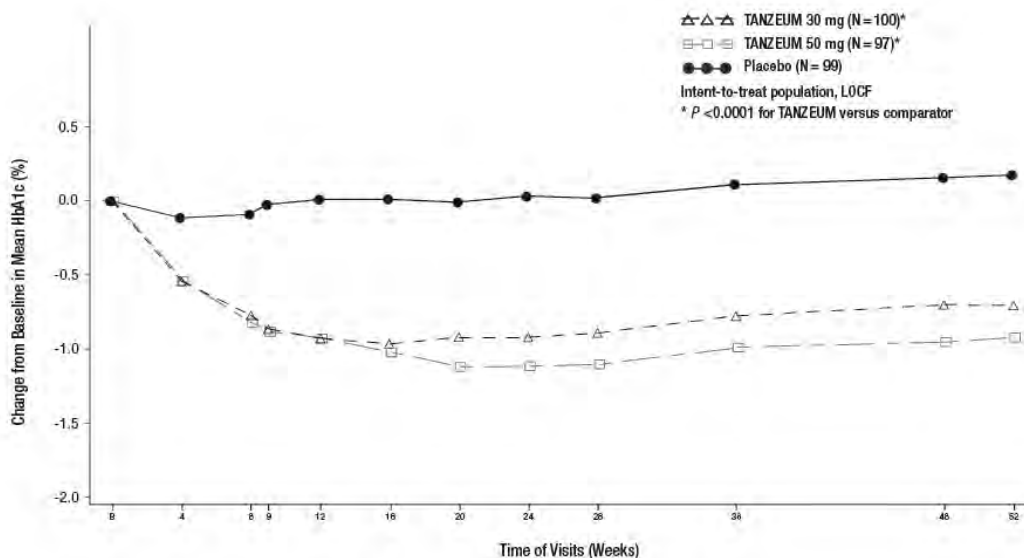
Table 4. Results at Week 52 (LOCF^a) in a Trial of TANZEUM as Monotherapy

	Placebo	TANZEUM 30 mg Weekly	TANZEUM 50 mg Weekly
ITT^a (N)	99	100	97
HbA1c (%)			
Baseline (mean)	8.0	8.1	8.2
Change at Week 52 ^b	+0.2	-0.7	-0.9
Difference from placebo ^b (95% CI)		-0.8 (-1.1, -0.6) ^c	-1.0 (-1.3, -0.8) ^c
Patients (%) achieving HbA1c <7%	21	49	40
FPG (mg/dL)			
Baseline (mean)	163	164	171
Change at Week 52 ^b	+18	-16	-25
Difference from placebo ^b (95% CI)		-34 (-46, -22) ^c	-43 (-55, -31) ^c

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 52, primary efficacy data was imputed for 63%, 34%, and 41% of individuals randomized to placebo, TANZEUM 30 mg, and TANZEUM 50 mg.

^b Least squares mean adjusted for baseline value and stratification factors.

^c $P < 0.0001$ for treatment difference.

Figure 1. Mean HbA1c Change from Baseline (ITT Population-LOCF) in a Trial of TANZEUM as Monotherapy

14.2 Combination Therapy

Add-on to Metformin

The efficacy of TANZEUM was evaluated in a 104-week randomized, double-blind, multicenter trial in 999 patients with type 2 diabetes mellitus inadequately controlled on background metformin therapy ($\geq 1,500$ mg daily). In this trial, TANZEUM 30 mg SC weekly (with optional

uptitration to 50 mg weekly after a minimum of 4 weeks) was compared with placebo, sitagliptin 100 mg daily, or glimepiride 2 mg daily (with optional titration to 4 mg daily). The mean age of participants was 55 years, 48% of patients were men, the mean duration of type 2 diabetes was 6 years, and the mean baseline eGFR was 86 mL/min/1.73 m². Results of the primary and secondary analyses are presented in Table 5. Figure 2 shows the mean adjusted changes in HbA1c across study visits.

Reduction in HbA1c from baseline achieved with TANZEUM was significantly greater than HbA1c reduction achieved with placebo, sitagliptin, and glimepiride at Week 104 (see Table 5). The difference in body weight change from baseline between TANZEUM and glimepiride was significant at Week 104.

Table 5. Results at Week 104 (LOCF^a) in a Trial Comparing TANZEUM with Placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin

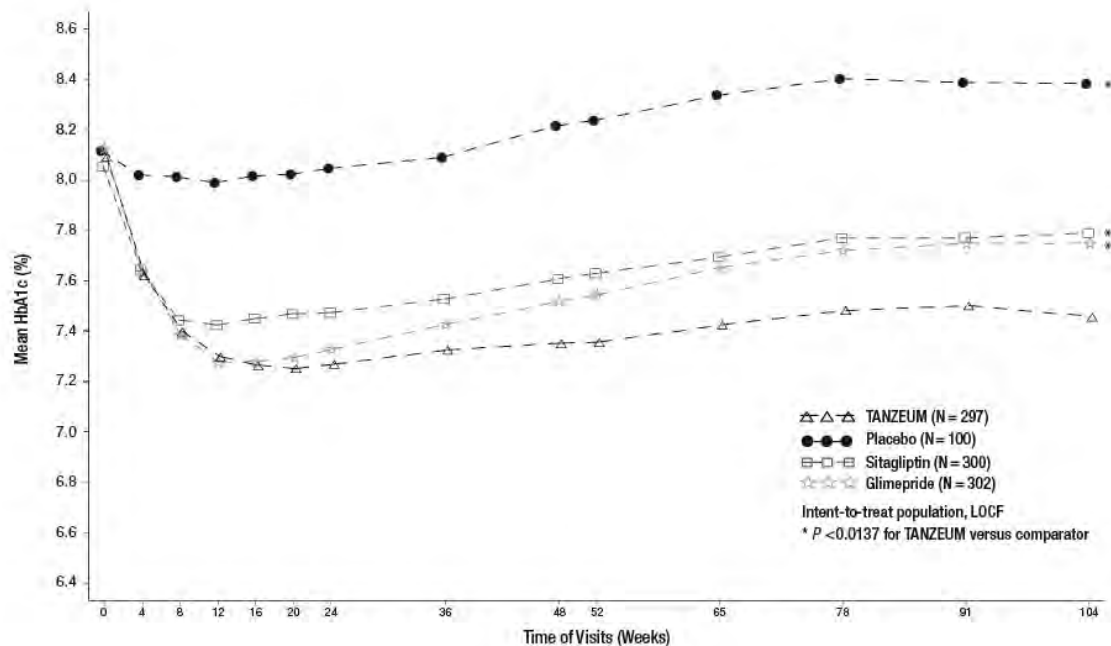
	TANZEUM + Metformin	Placebo + Metformin	Sitagliptin + Metformin	Glimepiride + Metformin
ITT^a (N)	297	100	300	302
HbA1c (%)				
Baseline (mean)	8.1	8.1	8.1	8.1
Change at Week 104 ^b	-0.6	+0.3	-0.3	-0.4
Difference from placebo + metformin ^b (95% CI)	-0.9 (-1.16, -0.65) ^c			
Difference from sitagliptin + metformin ^b (95% CI)	-0.4 (-0.53, -0.17) ^c			
Difference from glimepiride + metformin ^b (95% CI)	-0.3 (-0.45, -0.09) ^c			
Proportion achieving HbA1c <7%	39	16	32	31
FPG (mg/dL)				
Baseline (mean)	165	162	165	168
Change at Week 104 ^b	-18	+10	-2	-8
Difference from placebo + metformin ^b (95% CI)	-28 (-39, -16) ^c			
Difference from sitagliptin + metformin ^b (95% CI)	-16 (-24, -8) ^c			
Difference from glimepiride + metformin ^b (95% CI)	-10 (-18, -2) ^c			
Body Weight (kg)				
Baseline (mean)	90	92	90	92
Change at Week 104 ^b	-1.2	-1.0	-0.9	+1.2
Difference from placebo + metformin ^b (95% CI)	-0.2 (-1.1, 0.7)			
Difference from sitagliptin + metformin ^b (95% CI)	-0.4 (-1.0, 0.3)			
Difference from glimepiride + metformin ^b (95% CI)	-2.4 (-3.0, -1.7) ^c			

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 104, primary efficacy data was imputed for 76%, 46%, 55%, and 51% of individuals randomized to placebo, TANZEUM, sitagliptin, and glimepiride, respectively.

^b Least squares mean adjusted for baseline value and stratification factors.

^c *P* <0.0137 for treatment difference.

Figure 2. Mean HbA1c Over Time (ITT Population-LOCF) in a Trial Comparing TANZEUM with Placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin



Add-on to Pioglitazone

The efficacy of TANZEUM was evaluated in a 52-week randomized, double-blind, multicenter trial in 299 patients with type 2 diabetes mellitus inadequately controlled on pioglitazone ≥ 30 mg daily (with or without metformin $\geq 1,500$ mg daily). Patients were randomized to receive TANZEUM 30 mg SC weekly or placebo. The mean age of participants was 55 years, 60% of patients were men, the mean duration of type 2 diabetes was 8 years, and the mean baseline eGFR was 83 mL/min/1.73 m². Results of the primary and secondary analyses are presented in Table 6.

Compared with placebo, treatment with TANZEUM resulted in a statistically significant reduction in HbA1c from baseline at Week 52 (see Table 6). The adjusted mean change from baseline in weight did not differ significantly between TANZEUM (+0.3 kg) and placebo (+0.5 kg) at Week 52.

Table 6. Results at Week 52 (LOCF^a) in a Trial Comparing TANZEUM with Placebo as Add-on Therapy in Patients Inadequately Controlled on Pioglitazone (with or without Metformin)

	TANZEUM + Pioglitazone (with or without Metformin)	Placebo + Pioglitazone (with or without Metformin)
ITT^a (N)	150	149
HbA1c (%)		
Baseline (mean)	8.1	8.1
Change at Week 52 ^b	-0.8	-0.1
Difference from placebo + pioglitazone ^b (95% CI)	-0.8 (-0.95, -0.56) ^c	
Proportion Achieving HbA1c <7%	44	15
FPG (mg/dL)		
Baseline (mean)	165	167
Change at Week 52 ^b	-23	+6
Difference from placebo + pioglitazone ^b (95% CI)	-30 (-39, -20) ^c	

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 52, primary efficacy data was imputed for 58% and 32% of individuals randomized to placebo and TANZEUM, respectively.

^b Least squares mean adjusted for baseline value and stratification factors.

^c $P < 0.0001$ for treatment difference.

Add-on to Metformin Plus Sulfonylurea

The efficacy of TANZEUM was evaluated in a 52-week randomized, double-blind, multicenter trial in 657 patients with type 2 diabetes mellitus inadequately controlled on metformin ($\geq 1,500$ mg daily) and glimepiride (4 mg daily). Patients were randomized to receive TANZEUM 30 mg SC weekly (with optional uptitration to 50 mg weekly after a minimum of 4 weeks), placebo, or pioglitazone 30 mg daily (with optional titration to 45 mg/day). The mean age of participants was 55 years, 53% of patients were men, the mean duration of type 2 diabetes was 9 years, and the mean baseline eGFR was 84 mL/min/1.73 m². Results of the primary and main secondary analyses are presented in Table 7.

Treatment with TANZEUM resulted in statistically significant reductions in HbA1c from baseline compared with placebo (see Table 7). Treatment with TANZEUM did not meet the pre-specified, non-inferiority margin (0.3%) against pioglitazone. In this trial, TANZEUM provided less HbA1c reduction than pioglitazone and the treatment difference was statistically significant (see Table 7). The change from baseline in body weight for TANZEUM did not differ significantly from placebo but was significantly different compared with pioglitazone (see Table 7).

Table 7. Results at Week 52 (LOCF^a) in a Trial Comparing TANZEUM with Placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin Plus Sulfonylurea

	TANZEUM + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Pioglitazone + Metformin + Glimepiride
ITT^a (N)	269	115	273
HbA1c (%)			
Baseline (mean)	8.2	8.3	8.3
Change at Week 52 ^b	-0.6	+0.3	-0.8
Difference from placebo + met + glim ^b (95% CI)	-0.9 (-1.07, -0.68) ^c		
Difference from pioglitazone + met + glim ^b (95% CI)	0.25 (0.10, 0.40) ^d		
Proportion achieving HbA1c <7%	30	9	35
FPG (mg/dL)			
Baseline (mean)	171	174	177
Change at Week 52 ^b	-12	+12	-31
Difference from placebo + met + glim ^b (95% CI)	-24 (-34, -14) ^c		
Difference from pioglitazone + met + glim ^b (95% CI)	19 (11, 27) ^c		
Body Weight (kg)			
Baseline (mean)	91	90	91
Change at Week 52 ^b	-0.4	-0.4	+4.4
Difference from placebo + met + glim ^b (95% CI)	-0.0 (-0.9, 0.8)		
Difference from pioglitazone + met + glim ^b (95% CI)	-4.9 (-5.5, -4.2) ^c		

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 52, primary efficacy data was imputed for 70%, 35%, and 34% of individuals randomized to placebo, TANZEUM, and pioglitazone.

^b Least squares mean adjusted for baseline value and stratification factors.

^c $P < 0.0001$ for treatment difference.

^d Did not meet non-inferiority margin of 0.3%.

Combination Therapy: Active-controlled Trial versus Liraglutide

The efficacy of TANZEUM was evaluated in a 32-week, randomized, open-label, liraglutide-controlled, non-inferiority trial in 805 patients with type 2 diabetes mellitus inadequately controlled on monotherapy or combination oral antidiabetic therapy (metformin, thiazolidinedione, sulfonylurea, or a combination of these). Patients were randomized to TANZEUM 30 mg SC weekly (with up titration to 50 mg weekly at Week 6) or liraglutide 1.8 mg daily (titrated up from 0.6 mg at Week 1, and 1.2 mg at Week 1 to Week 2). The mean age of participants was 56 years, 50% of patients were men, the mean duration of type 2 diabetes was 8 years, and the mean baseline eGFR was 95 mL/min/1.73 m². Results of the primary and main secondary analyses are presented in Table 8.

The between-treatment difference of 0.2% with 95% confidence interval (0.08, 0.34) between TANZEUM and liraglutide did not meet the pre-specified, non-inferiority margin (0.3%). In this trial, TANZEUM provided less HbA1c reduction than liraglutide and the treatment difference was statistically significant (see Table 8).

Table 8. Results of Controlled Trial of TANZEUM versus Liraglutide at Week 32 (LOCF^a)

	TANZEUM	Liraglutide
ITT^a (N)	402	403
HbA1c (%)		
Baseline (mean)	8.2%	8.2%
Change at Week 32 ^b	-0.8	-1.0
Difference from liraglutide ^b (95% CI)	0.2 (0.08, 0.34) ^c	
Proportion achieving HbA1c <7%	42%	52%
FPG (mg/dL)		
Baseline (mean)	169	167
Change at Week 32 ^b	-22	-30
Difference from liraglutide ^b (95% CI)	8 (3, 14) ^d	
Body Weight (kg)		
Baseline (mean)	92	93
Change at Week 32 ^b	-0.6	-2.2
Difference from liraglutide ^b (95% CI)	1.6 (1.1, 2.1) ^d	

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 32, primary efficacy data was imputed for 31% and 24% of individuals randomized to TANZEUM and liraglutide.

^b Least squares mean adjusted for baseline value and stratification factors.

^c Did not meet non-inferiority margin of 0.3%.

^d $P < 0.005$ for treatment difference in favor of liraglutide.

Combination Therapy: Active-controlled Trial versus Basal Insulin

The efficacy of TANZEUM was evaluated in a 52-week, randomized (2:1), open-label, insulin glargine-controlled, non-inferiority trial in 735 patients with type 2 diabetes mellitus inadequately controlled on metformin $\geq 1,500$ mg daily (with or without sulfonylurea). Patients were randomized to receive TANZEUM 30 mg SC weekly (with optional uptitration to 50 mg weekly) or insulin glargine (started at 10 units and titrated weekly per prescribing information). The primary endpoint was change in HbA1c from baseline compared with insulin glargine. The starting total daily dose of insulin glargine ranged between 2 and 40 units (median daily dose of 10 units) and ranged between 3 and 230 units (median daily dose of 30 units) at Week 52. Seventy-seven percent of patients treated with TANZEUM were uptitrated to 50 mg SC weekly. The mean age of participants was 56 years, 56% of patients were men, the mean duration of type

2 diabetes was 9 years, and the mean baseline eGFR was 85 mL/min/1.73 m². Results of the primary and main secondary analyses are presented in Table 9.

The between-treatment difference of 0.1% with 95% confidence interval (-0.04%, 0.27%) for TANZEUM and insulin glargine met the pre-specified, non-inferiority margin (0.3%). A mean decrease in body weight was observed for TANZEUM compared with a mean increase in body weight for insulin glargine, and the difference in weight change was statistically significant (see Table 9).

Table 9. Results at Week 52 (LOCF^a) in a Trial Comparing TANZEUM with Insulin Glargine as Add-on Therapy in Patients Inadequately Controlled on Metformin ± Sulfonylurea

	TANZEUM + Metformin (with or without Sulfonylurea)	Insulin Glargine + Metformin (with or without Sulfonylurea)
ITT^a (N)	496	239
HbA1c (%)		
Baseline (mean)	8.3	8.4
Change at Week 52 ^b	-0.7	-0.8
Difference from insulin glargine ^b (95% CI)	0.1 (-0.04, 0.27) ^c	
Proportion achieving HbA1c <7%	32	33
FPG (mg/dL)		
Baseline (mean)	169	175
Change at Week 52 ^b	-16	-37
Difference from insulin glargine ^b (95% CI)	21 (14, 29) ^d	
Body Weight (kg)		
Baseline (mean)	95	95
Change at Week 52 ^b	-1.1	1.6
Difference from insulin glargine ^b (95% CI)	-2.6 (-3.2, -2.0) ^e	

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 52, primary efficacy data was imputed for 41% and 36% of individuals randomized to TANZEUM and insulin glargine.

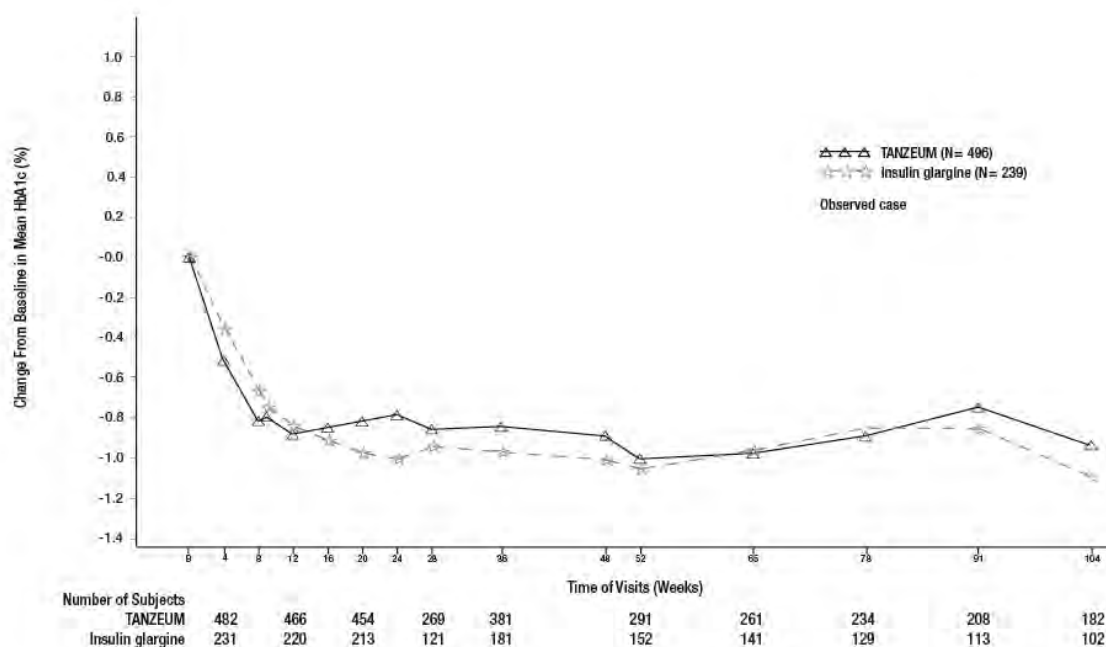
^b Least squares mean adjusted for baseline value and stratification factors.

^c Met non-inferiority margin of 0.3%.

^d *P* <0.0001 in favor of insulin glargine.

^e *P* <0.0001.

Figure 3. Mean HbA1c Change from Baseline (Completers) in a Trial Comparing TANZEUM with Insulin Glargine as Add-on Therapy in Patients Inadequately Controlled on Metformin (with or without a Sulfonylurea)



Combination Therapy: Active-controlled Trial versus Prandial Insulin

The efficacy of TANZEUM was evaluated in a 26-week, randomized, open-label, multicenter, non-inferiority trial in 563 patients with type 2 diabetes mellitus inadequately controlled on insulin glargine (started at 10 units and titrated to ≥ 20 units per day). Patients were randomized to receive TANZEUM 30 mg SC once weekly (with uptitration to 50 mg if inadequately controlled after Week 8) or insulin lispro (administered daily at meal times, started according to standard of care and titrated to effect). At Week 26, the mean daily dose of insulin glargine was 53 IU for TANZEUM and 51 IU for insulin lispro. The mean daily dose of insulin lispro at Week 26 was 31 IU, and 69% of patients treated with TANZEUM were on 50 mg weekly. The mean age of participants was 56 years, 47% of patients were men, the mean duration of type 2 diabetes was 11 years, and the mean baseline eGFR was 91 mL/min/1.73 m². Results of the primary and main secondary analyses are presented in Table 10. Figure 4 shows the mean adjusted changes in HbA1c from baseline across study visits.

The between-treatment difference of -0.2% with 95% confidence interval (-0.32%, 0.00%) between albiglutide and insulin lispro met the pre-specified non-inferiority margin (0.4%). Treatment with TANZEUM resulted in a mean weight loss for TANZEUM compared with a mean weight gain for insulin lispro, and the difference between treatment groups was statistically significant (see Table 10).

Table 10. Results at Week 26 (LOCF^a) in a Trial Comparing TANZEUM with Insulin Lispro as Add-On Therapy in Patients Inadequately Controlled on Insulin Glargine

	TANZEUM + Insulin Glargine	Insulin Lispro + Insulin Glargine
ITT^a (N)	282	281
HbA_{1c} (%)		
Baseline (mean)	8.5	8.4
Change at Week 26 ^b	-0.8	-0.7
Difference from insulin lispro ^b (95% CI)	-0.2 (-0.32, 0.00) ^c	
Proportion achieving HbA _{1c} <7%	30%	25%
FPG (mg/dL)		
Baseline (mean)	153	153
Change at Week 26 ^b	-18	-13
Difference from insulin lispro ^b (95% CI)	-5 (-13, 3)	
Body Weight (kg)		
Baseline (mean)	93	92
Change at Week 26 ^b	-0.7	+0.8
Difference from insulin lispro ^b (95% CI)	-1.5 (-2.1, -1.0) ^d	

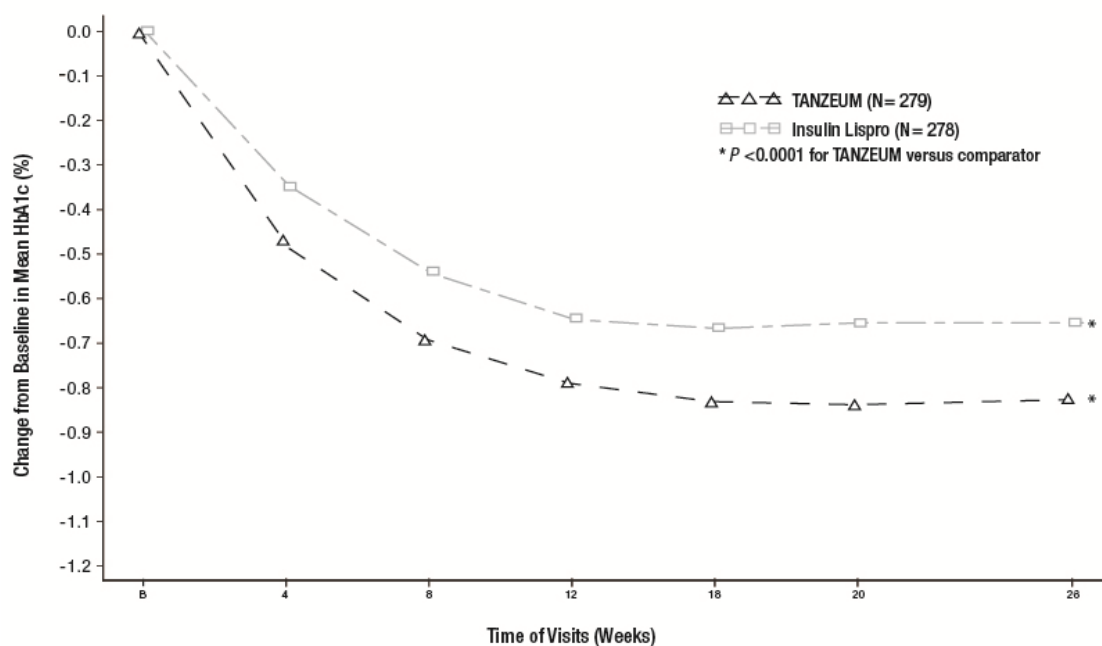
^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 26, primary efficacy data was imputed for 29% and 29% of individuals randomized to TANZEUM and insulin lispro.

^b Least squares mean adjusted for baseline value and stratification factors.

^c Rules out a non-inferiority margin of 0.4%.

^d $P < 0.0001$ for treatment difference.

Figure 4. Mean HbA1c Change from Baseline (ITT-LOCF population) in a Trial Comparing TANZEUM with Insulin Lispro as Add-On Therapy in Patients Inadequately Controlled on Insulin Glargine



14.3 Type 2 Diabetes Mellitus Patients with Renal Impairment

The efficacy of TANZEUM was evaluated in a 26-week, randomized, double-blind, active-controlled trial in 486 patients with mild ($n = 250$), moderate ($n = 200$), and severe renal impairment ($n = 36$) inadequately controlled on a current regimen of diet and exercise or other antidiabetic therapy. Patients were randomized to receive TANZEUM 30 mg SC weekly (with uptitration to 50 mg weekly if needed as early as Week 4) or sitagliptin. Sitagliptin was dosed according to renal function (100 mg, 50 mg, and 25 mg daily in mild, moderate, and severe renal impairment, respectively). The mean age of participants was 63 years, 54% of patients were men, the mean duration of type 2 diabetes was 11 years, and the mean baseline eGFR was 60 mL/min/1.73 m².

Results of the primary and main secondary analyses are presented in Table 11. Treatment with TANZEUM resulted in statistically significant reductions in HbA1c from baseline at Week 26 compared with sitagliptin (see Table 11).

Table 11. Results at Week 26 (LOCF^a) in a Trial Comparing TANZEUM with Sitagliptin in Patients with Renal Impairment

	TANZEUM	Sitagliptin
ITT^a (N)	246	240
HbA1c (%)		
Baseline (mean)	8.1	8.2
Change at Week 26 ^b	-0.8	-0.5
Difference from sitagliptin ^b (95% CI)	-0.3 (-0.49, -0.15) ^c	
Proportion achieving HbA1c <7%	43%	31%
FPG (mg/dL)		
Baseline (mean)	166	165
Change at Week 26 ^b	-26	-4
Difference from sitagliptin ^b (95% CI)	-22 (-31, -13) ^c	
Body Weight (kg)		
Baseline (mean)	84	83
Change at Week 26 ^b	-0.8	-0.2
Difference from sitagliptin ^b (95% CI)	-0.6 (-1.1, -0.1) ^d	

^a Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 26 primary efficacy data was imputed for 17% and 25% of individuals randomized to TANZEUM and sitagliptin.

^b Least squares mean adjusted for baseline value and stratification factors.

^c $P < 0.0003$ for treatment difference.

^d $P = 0.0281$ for treatment difference.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TANZEUM is available in the following strengths and package size:

30 mg single-dose Pen (NDC 0173-0866-01):

- carton of 4 (containing four 29-gauge, 5-mm, thinwall needles): NDC 0173-0866-35

50 mg single-dose Pen (NDC 0173-0867-01):

- carton of 4 (containing four 29-gauge, 5-mm, thinwall needles): NDC 0173-0867-35

16.2 Storage and Handling

- Prior to dispensing: Store Pens in the refrigerator at 36°F to 46°F (2°C to 8°C). Pens may be stored refrigerated until the expiration date.
- Following dispensing: Store Pens in the refrigerator at 36°F to 46°F (2°C to 8°C). Patients may store Pens at room temperature not to exceed 86°F (30°C) for up to 4 weeks prior to use. Store Pens in the original carton until use.

- Do not freeze.
- Do not use past the expiration date.
- Use within 8 hours after reconstitution.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use). The Medication Guide is contained in a separate leaflet that accompanies the product.

- Inform patients about self-management practices, including the importance of proper storage of TANZEUM, injection technique, timing of dosage of TANZEUM and concomitant oral drugs, and recognition and management of hypoglycemia.
- Inform patients that thyroid C-cell tumors have been observed in rodents treated with some GLP-1 receptor agonists, and the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors to their physician [*see Warnings and Precautions (5.1)*].
- Advise patients that persistent, severe abdominal pain that may radiate to the back and which may (or may not) be accompanied by vomiting is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TANZEUM promptly and to contact their physician if persistent, severe abdominal pain occurs [*see Warnings and Precautions (5.2)*].
- The risk of hypoglycemia is increased when TANZEUM is used in combination with an agent that induces hypoglycemia, such as sulfonylurea or insulin. Instructions for hypoglycemia should be reviewed with patients and reinforced when initiating therapy with TANZEUM, particularly when concomitantly administered with a sulfonylurea or insulin [*see Warnings and Precautions (5.3)*].
- Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TANZEUM and seek medical advice promptly if such symptoms occur [*see Warnings and Precautions (5.4)*].
- Instruct patients to read the Instructions for Use before starting therapy. Instruct patients on proper use, storage, and disposal of the pen [*see How Supplied/Storage and Handling (16.2), Patient Instructions for Use*].
- Instruct patients to read the Medication Guide before starting TANZEUM and to read again each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.
- Inform patients not to take an extra dose of TANZEUM to make up for a missed dose. If a dose is missed, instruct patients to take a dose as soon as possible within 3 days after the missed dose. Instruct patients to then take their next dose at their usual weekly time. If it has been longer than 3 days after the missed dose, instruct patients to wait and take TANZEUM at the next usual weekly time.

TANZEUM is a trademark of the GSK group of companies.



Manufactured by **GlaxoSmithKline LLC**

Wilmington, DE 19808

U.S. Lic. No. 1727

Marketed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

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TNZ:3PI

MEDICATION GUIDE
TANZEUM™ (TAN-zee-um)
(albiglutide)
for injection, for subcutaneous use

Read this Medication Guide before you start taking TANZEUM and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about TANZEUM?

Serious side effects may happen in people who take TANZEUM, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, medicines that work like TANZEUM caused thyroid tumors, including thyroid cancer. It is not known if TANZEUM will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma in people.
- **Do not use TANZEUM if you** or your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system cancer called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is TANZEUM?

TANZEUM is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.

- TANZEUM is not recommended as the first choice of medicine for treating diabetes.
- It is not known if TANZEUM can be used in people who previously had pancreatitis.
- TANZEUM is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- TANZEUM is not recommended in people with severe stomach or intestinal problems.
- It is not known if TANZEUM can be used with short-acting or rapid-acting (mealtime) insulin.
- It is not known if TANZEUM is safe and effective in children under 18 years of age.

Who should not use TANZEUM?

Do not use TANZEUM if:

- you or your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system cancer called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- you are allergic to albiglutide or any of the ingredients in TANZEUM.

Before using TANZEUM, tell your healthcare provider about your medical conditions including, if you:

- have or have had problems with your pancreas, kidneys, or liver
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food
- are pregnant or plan to become pregnant. It is not known if TANZEUM will harm your unborn baby. Tell your healthcare provider if you become pregnant while using TANZEUM.
- are breastfeeding or plan to breastfeed. It is not known if TANZEUM passes into your breast milk. You and your healthcare provider should decide if you will use TANZEUM or breastfeed. You should not do both without talking with your healthcare provider first.
- are taking a new prescription or over-the-counter medicines, vitamins, or herbal supplements.

How should I use TANZEUM?

- Read the **Instructions for Use** that comes with TANZEUM.
- Use TANZEUM exactly as your healthcare provider tells you to.
- **Use TANZEUM 1 time each week on the same day each week at any time of the day.**
- You may change your day of the week as long as your last dose was given **4** or more days before.
- If you miss a dose of TANZEUM, take the missed dose of TANZEUM within **3** days after your usual scheduled day. If more than **3** days have gone by since your missed dose, wait until your next regularly scheduled weekly dose.
- TANZEUM may be taken with or without food.
- **Do not mix insulin and TANZEUM together in the same injection.**
- **Do not share your pen or needles with another person.** You may give another person an infection or get an infection from them.

What are the possible side effects of TANZEUM?

TANZEUM may cause serious side effects, including:

- **inflammation of your pancreas (pancreatitis).** Stop using TANZEUM and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel pain that may go from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk is higher if you take TANZEUM with another medicine that can cause low blood sugar such as insulin or sulfonylurea. Signs and symptoms of low blood sugar may include:
 - dizziness or light-headedness
 - blurred vision
 - anxiety, irritability, or mood changes
 - sweating
 - slurred speech
 - hunger
 - confusion
 - shakiness
 - feeling jittery
 - headache
 - fast heart beat
- **allergic reactions.** Stop using TANZEUM and get medical help right away if you have any symptoms of an allergic reaction including itching, rash, or difficulty breathing.
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may result in loss of fluids (dehydration) which may worsen kidney problems.

Common side effects of TANZEUM may include diarrhea, nausea, reactions at your injection site, cough, back pain, and cold or flu symptoms.

These are not all the possible side effects of TANZEUM. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TANZEUM.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TANZEUM that is written for health professionals. Do not use TANZEUM for a condition for which it was not prescribed. Do not give TANZEUM to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in TANZEUM?

Active Ingredient: albiglutide

Inactive Ingredients: mannitol, polysorbate 80, sodium phosphate, and trehalose dihydrate. TANZEUM does not contain a preservative.

For more information, go to www.TANZEUM.com or call 1-888-825-5249.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approved: April 2014



GlaxoSmithKline

Manufactured by **GlaxoSmithKline LLC**
Wilmington, DE 19808
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Marketed by GlaxoSmithKline
Research Triangle Park, NC 27709

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TNZ:1MG

INSTRUCTIONS FOR USE

TANZEUM™ (TAN-zee-um) (albiglutide)

for injection, for subcutaneous use

TANZEUM (albiglutide) Pen 30 mg

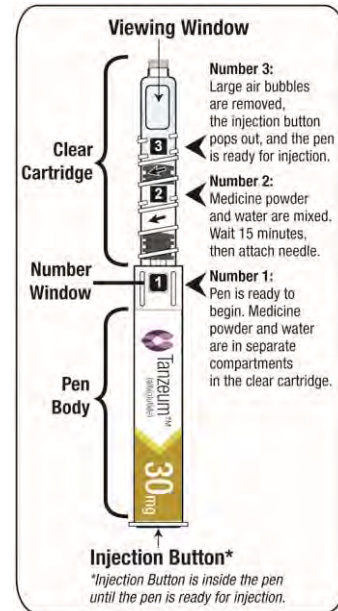
Use 1 Time Each Week

Read all the instructions and follow the steps below to mix the medicine and prepare the pen for injection.

Failure to follow Steps A to C in the correct order may result in damage to your pen.

Information About This Pen

- This medicine is injected **1** time each week.
- The pen has medicine powder in 1 compartment and water in another compartment. You will need to mix them together by twisting the pen, then wait for **15** minutes for the medicine and water to fully mix.



CAUTION:

Do not allow the pen to freeze. Throw away the pen if frozen.

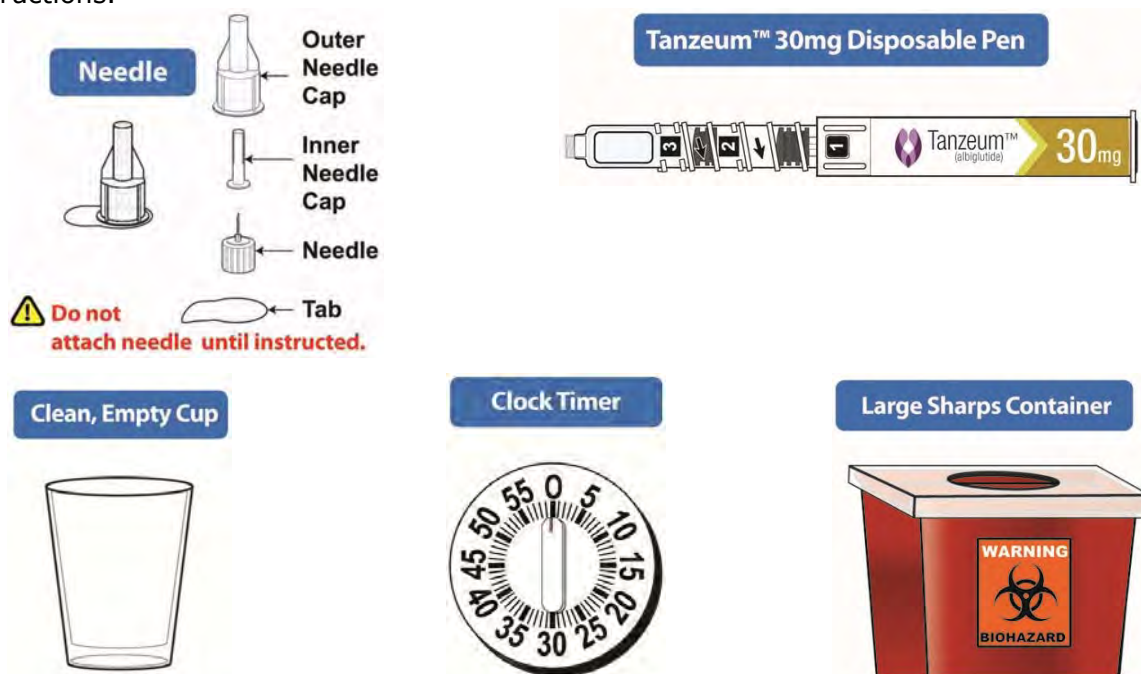
If stored in refrigerator, allow to sit at room temperature for 15 minutes before starting Step A.

Dispose of the pen right away after injecting. Do not recap, remove, or reuse the needle.

Before you Begin: Wash Your Hands, Gather and Inspect Your Supplies

- Wash your hands.
- Take a pen and new needle out of the box and check the label on your pen to make sure it is your prescribed dose of medicine.

- Gather a **clean, empty cup** to hold the pen while the medicine mixes, a **clock timer** to measure the time while the medicine mixes, and a large **sharps container** for pen disposal. See “**Disposing of Your Used Pens and Needles**” at the end of these instructions.

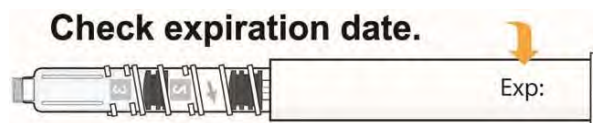


STEP A

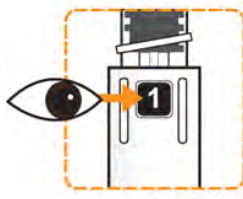
Inspect Your Pen and Mix Your Medicine

Inspect Your Pen

- Make sure that you have all of the supplies listed above (pen, needle, cup, timer, sharps container).
- Check the expiration date on the pen. **Do not** use if expired.



- Check that the pen has a **[1]** in the number window. **Do not** use if the **[1]** is not showing.

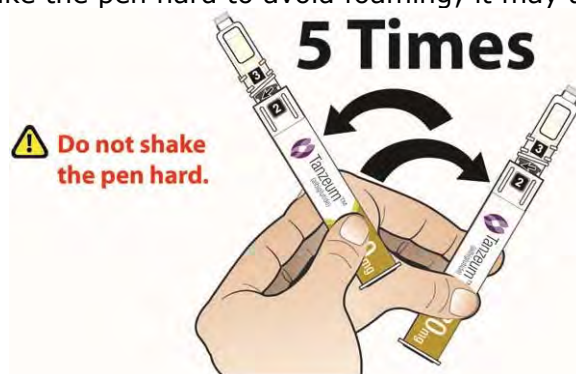


Twist Pen to Mix Your Medicine

- Hold the pen body with the clear cartridge pointing up so that you **see the [1] in the number window**.
- With your other hand, twist the clear cartridge several times in the direction of the arrow (clockwise) until you feel and hear the pen “click” into place and you **see the [2] in the number window**. This will mix the medicine powder and liquid in the clear cartridge.



- Slowly and gently rock the pen side to side (like a windshield wiper) **5 times** to mix the medicine. **Do not** shake the pen hard to avoid foaming; it may affect your dose.



Wait for Medicine to Dissolve

- Place the pen into the clean, empty cup to keep the clear cartridge pointing up.
- **Set the clock timer for 15 minutes.**



You must wait 15 minutes for the medicine to dissolve before continuing to Step B.

STEP B

Attach the Needle and Prepare the Pen for Injection

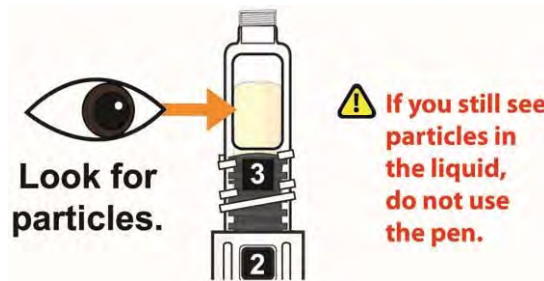
After the 15 minute wait, wash your hands and finish the rest of the steps right away.

Inspect Your Dissolved Medicine

- Again, slowly and gently rock the pen side to side (like a windshield wiper) **5** times to mix the medicine again. **Do not** shake the pen hard to avoid foaming; it may affect your dose.



- Look through the viewing window to check that the liquid in the cartridge is clear and free of solid particles.



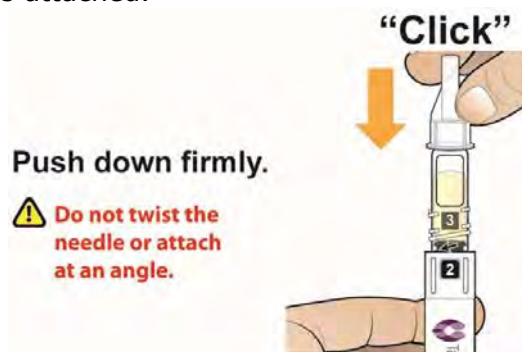
- The liquid will have a yellow color and there will be **large air bubbles** on top of the liquid.

Attach the Needle

- Peel the tab from the outer needle cap.



- Hold the pen with the clear cartridge pointing up and push the needle straight down onto the clear cartridge until you hear a “click” and feel the needle “snap” down into place. This means the needle is attached.



Tap for Air Bubbles

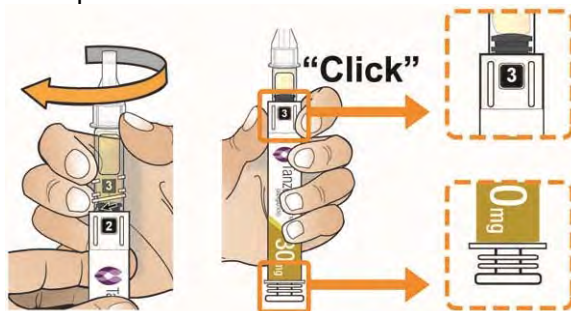
- With the needle point up, gently tap the clear cartridge **2 to 3** times to bring large air bubbles to the top.



Small bubbles are okay and do not need to rise to the top.

Twist Pen to Prime the Needle

- Twist the clear cartridge several times in the direction of the arrow (clockwise) until you feel and hear the pen “click” and you **see the [3] in the number window**. This removes the large air bubbles from the clear cartridge. The injection button will also pop out from the bottom of the pen.

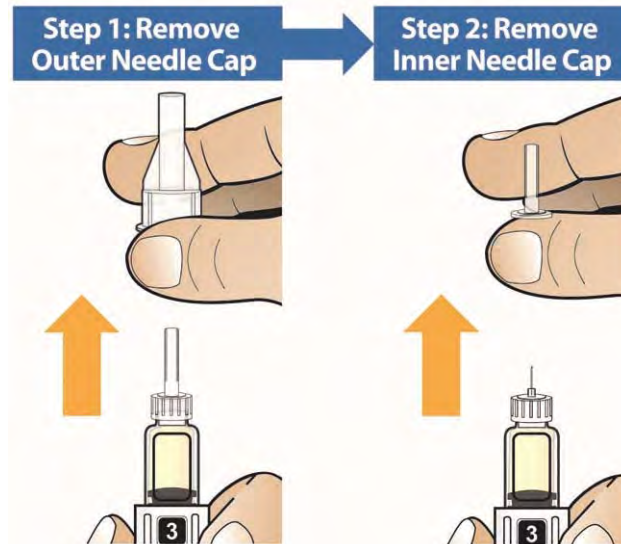


STEP C

Remove Both Needle Caps and Inject Your Medicine

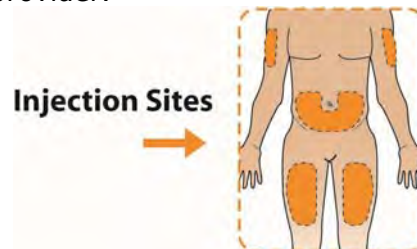
Remove Needle Caps

- Carefully remove the outer needle cap, then the inner needle cap. **A few drops of liquid may come out of the needle. This is normal.**

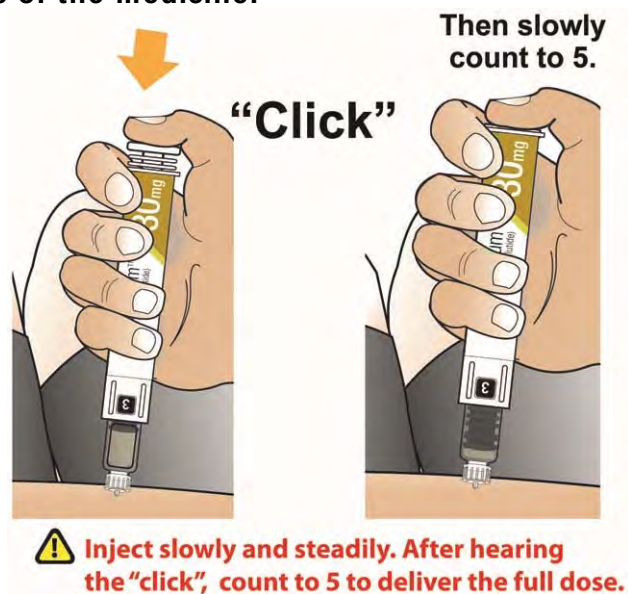


Inject the Medicine

- Insert the needle into the skin on your abdomen, thigh, or upper arm and inject as shown to you by your healthcare provider.



- With your thumb, press the injection button slowly and steadily to inject your medicine. The slower you press the button, the less pressure you will feel.
- Keep the injection button pressed down until you hear a “click”. **After hearing the click, continue holding your thumb down on the button and then slowly count to 5 to deliver the full dose of the medicine.**



- After hearing the “click” and then slowly counting to **5**, pull the needle out of your skin.

Disposing of Your Used Pens and Needles

- **Do not** recap the needle or remove needle from the pen.
- Put your used needles and pens in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and pens in your household trash.**



General Information About the Safe and Effective Use of TANZEUM

- Take **1** time each week. You can take your medicine at any time of day, with or without meals.
- **Your healthcare provider will teach you how to mix and inject TANZEUM before you use it for the first time.** If you have questions or do not understand the **Instructions for Use**, talk to your healthcare provider.
- **Use TANZEUM exactly as your healthcare provider tells you. Do not** change your dose or stop TANZEUM without talking to your healthcare provider.
- **Change (rotate) your injection site with each injection (weekly).**
- TANZEUM is injected under the skin (subcutaneously) in your stomach area (abdomen), upper leg (thigh), or upper arm.
- **Do not** inject TANZEUM into a vein or muscle.
- If you use TANZEUM with insulin, you should inject your TANZEUM and insulin separately. **Do not mix insulin and TANZEUM together.** You can inject TANZEUM and insulin in the same body area (for example, your stomach area), but you should not give the injections right next to each other.
- Keep pens and needles out of the reach of children.
- Always use a new needle for each injection.
- Do not share pens or needles.

Frequently Asked Questions

Medicine Dosing

What if I need to take my medicine on a different day of the week?

- You may take your next dose of medicine on a different day as long as it has been at least **4** days since your last dose.

What if I forget to take the medicine on the day I am supposed to?

- Take your missed dose of medicine within **3** days after your scheduled day, then return to your scheduled day for your next dose. If more than **3** days have passed since your usual scheduled day, wait until your next regularly scheduled day to take the injection of TANZEUM.

Storage

How should I store my medicine?

- Store your pens in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store your pen in the box at room temperature below 86°F (30°C) for up to **4** weeks before you are ready to use the pen.
- Store pens in the carton they came in.

- **Do not** freeze pens. If the liquid in the pen is frozen, throw away the pen and use another pen.

Number Window

Are the Numbers 1, 2, and 3 used to select my dose of medicine?

- No, you do not have to select your dose. The numbers are to help you prepare and give your medicine.

Number 1: Pen is ready to begin. Medicine powder and water are in separate compartments in the clear cartridge. If you don't see a number **1** in the window, throw away the pen.

Number 2: Medicine powder and water are mixed and then gently rocked. Wait **15** minutes, then attach needle.

Number 3: Large air bubbles are removed, the injection button pops out, and the pen is ready for injection.

What if I do not hear the “click” when the 2 or 3 are moved into the Number Window?

- If you do not hear a “click” when **2 or 3** are moved into the number window, you may not have the number fully centered in the window. Twist the clear cartridge slightly in the direction of the arrow to complete the “click” and center the number in the window. Do not turn the clear cartridge in the opposite direction from the arrows.

Step A: Inspect Your Pen and Mix Your Medicine

What if I do not wait 15 minutes after turning the pen to the Number 2?

- If you do not wait the full **15** minutes the medicine may not be mixed with the water the right way. This can result in particles floating in the clear cartridge, not getting your full dose, or a blocked needle. Waiting the full **15** minutes ensures that the medicine powder and water are mixed the right way, even though it may look like it is mixed sooner than that.

What if I leave my pen for more than 15 minutes after turning the pen to the Number 2 in Step A?

- As long as the needle has not been attached, the pen can be used for up to **8** hours from the time **Step A** was started. If it has been more than **8** hours since the medicine was mixed in **Step A**, throw away the pen and use another pen.
- If you have attached the needle, TANZEUM should be used right away.

Step B: Attach the Needle and Prepare Pen for Injection

What if I leave my pen with the needle attached at Step B, and come back later to finish Step C?

- This can cause your needle to block, you should continue from **Step B** to **Step C** right away.

What if I do not attach the needle at Step B?

- If the needle is attached at **Step A**, some of the medicine may be lost during mixing. Throw away the pen and use another pen.
- If the needle is not attached before turning the pen from Position **2 to 3** in **Step B**, this can damage the pen.

Step C: Remove Both Needle Caps and Inject Your Medicine

After I turn the pen to Number 3 (Step B), there are still some small air bubbles remaining. Can I still use the pen?

- Seeing small air bubbles remaining is normal and you can still use the pen.

After I give my medicine, there is some liquid still seen in the clear cartridge.

- This is normal. If you have heard and felt the injection button “click” and slowly counted to **5** before pulling the needle out of your skin, you should have received the full dose of your medicine.

How should I dispose of the pen?

- **Do not** recap the needle or remove needle from the pen.
- Put your used needles and pens in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and pens in your household trash.**
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
 - o made of a heavy-duty plastic,
 - o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - o upright and stable during use,
 - o leak-resistant, and
 - o properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information

about sharps disposal in the state that you live in, go to the FDA's website at:

<http://www.fda.gov/safesharpsdisposal>.

- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.



**Please make sure you are using the right dose.
These instructions are for the 30 mg dose.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: June 2014

 GlaxoSmithKline	Manufactured by GlaxoSmithKline LLC Wilmington, DE 19808 U.S. Lic No. 1727 Marketed by GlaxoSmithKline Research Triangle Park, NC 27709	TANZEUM is a trademark of the GSK group of companies. ©2014, the GSK group of companies. All rights reserved. TNZ:2IFU-30
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Medication Guide

SYMLIN[®] (Sĭm-lĭn) (pramlintide acetate) injection

Read the Medication Guide that comes with SYMLIN before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about SYMLIN?

- **SYMLIN is used with insulin to lower blood sugar, especially high blood sugar that happens after meals.**
- **SYMLIN is given at mealtimes. The use of SYMLIN does not replace your daily insulin but may lower the amount of insulin you need, especially before meals.**
- **Even when SYMLIN is carefully added to your mealtime insulin therapy, your blood sugar may drop too low, especially if you have type 1 diabetes. If this low blood sugar (severe hypoglycemia) happens, it is seen within 3 hours after a SYMLIN injection. Severe low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others.**
- **SYMLIN should only be used by people with type 1 and type 2 diabetes who:**
 - already use their insulin as prescribed, but still need better blood sugar control.
 - will follow their doctor's instructions exactly.
 - will follow up with their doctor often.
 - will test their blood sugar levels before and after every meal, and at bedtime.
 - understand how to adjust SYMLIN and insulin doses.

What is SYMLIN?

SYMLIN is an injectable medicine for adults with type 1 and type 2 diabetes to control blood sugar. SYMLIN slows down the movement of food through your stomach. This affects how fast sugar enters your blood after eating. SYMLIN is always used with insulin to help lower blood sugar during the 3 hours after meals.

Who should not use SYMLIN?

Do not use SYMLIN if you:

- cannot tell when your blood sugar is low (hypoglycemia unawareness).
- have a stomach problem called gastroparesis. This is when your stomach does not empty as fast as it should.

- are allergic to SYMLIN or any ingredients in SYMLIN. See the end of this Medication Guide for a complete list of ingredients.

SYMLIN has not been studied in children.

What should I tell my doctor before starting SYMLIN?

Tell your doctor about all of your medical conditions including if you:

- **are pregnant or planning to become pregnant.** It is not known if SYMLIN can harm your unborn baby. You and your doctor will decide how to best control your blood sugar levels during pregnancy.
- **are breastfeeding.** It is not known if SYMLIN passes into your milk and if it can harm your baby. You and your doctor will decide the best way to feed your baby if you are using SYMLIN.

Keep a list of all the medicines you take. Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMLIN can slow down how other medicines pass through your stomach and may affect how much of them get into your body. Therefore, you may have to change the times you take certain medicines.

How should I use SYMLIN?

- **You must use SYMLIN exactly as prescribed. The amount of SYMLIN you use will depend on whether you have type 1 or type 2 diabetes.** You and your doctor will decide if you can use SYMLIN.
- **Never mix SYMLIN and insulin.** You must use different syringes for SYMLIN and insulin because insulin can affect SYMLIN when the two are mixed together.
- Injecting SYMLIN is similar to injecting insulin. **Inject SYMLIN under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).** Inject SYMLIN at a site that is more than 2 inches away from your insulin injection. Allow SYMLIN to warm to room temperature before injecting. Use a U-100 insulin syringe (best to use 0.3 mL [0.3 cc] size) to draw-up and inject SYMLIN. Always use a new syringe and needle for each SYMLIN injection.
- The dose of SYMLIN that your doctor prescribes should be one in Table 1. Use this table to match your SYMLIN dose to insulin syringe units.

Table 1: SYMLIN Dosing Chart

Find Your Dose in micrograms (mcg)	Draw Up This Amount in U-100 Insulin Syringe (units)
15	2½
30	5
45	7½
60	10
120	20

- Do not use SYMLIN if the liquid in the vial looks cloudy.
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and you may not be able to eat the amount of food you usually eat. Pay careful attention to the amount of insulin you use at this time as you may be at more risk for low blood sugar. Contact your doctor for guidance.
- If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of SYMLIN at that meal. Do not take more than your usual dose of SYMLIN.

Using SYMLIN and insulin with Type 2 Diabetes (see Table 1)

1. Start SYMLIN at 60 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. Reduce your rapid-acting or short-acting insulin doses before meals by **50 percent**, including fixed-mix insulins such as 70/30. This means half of the dose you usually use.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 120 mcg on your doctor's instructions if you have not had any nausea for 3 days or more.
5. Tell your doctor right away if you have nausea with the 120 mcg dose. Your doctor will tell you how to adjust your dose of SYMLIN.
6. Your doctor may make changes to your insulin doses to better control your blood sugar once you are using the 120 mcg dose of SYMLIN. All insulin changes should be directed by your doctor.

Using SYMLIN and insulin with Type 1 Diabetes (see Table 1)

1. Start SYMLIN at 15 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. When starting SYMLIN, reduce your rapid-acting or short-acting insulin doses before meals by **50 percent**, including fixed-mix insulins such as 70/30. This means half of the dose you usually use. All insulin changes should be directed by your doctor.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 30 mcg on your doctor's instructions if you have not had any nausea for 3 days or more. If you have nausea with SYMLIN at 30 mcg, call your doctor right away. Your doctor may decide that you should stop SYMLIN.
5. Increase your dose of SYMLIN to 45 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 30 mcg dose.
6. Increase your dose of SYMLIN to 60 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 45 mcg dose.
7. Call your doctor right away if you are bothered with nausea on the 45 mcg or 60 mcg dose. Your doctor may decide that you should reduce SYMLIN to the 30 mcg dose.

8. Your doctor may make changes to your insulin doses to better control your blood sugar once you are on a dose of SYMLIN that is right for you. All insulin changes should be directed by your doctor.

Staying on SYMLIN

- Once you reach your recommended dose of SYMLIN, talk to your doctor about changing your insulin doses to better control your blood sugar. You may have to increase your long-acting insulin to prevent high blood sugar (hyperglycemia) between meals. **Insulin changes should be directed by your doctor based on blood sugar testing.**
- Call your doctor if nausea or low blood sugar continues while on your recommended dose of SYMLIN. Low blood sugar that happens often is a warning sign of possible severe low blood sugar, especially if you have type 1 diabetes.
- **If you stop taking SYMLIN for any reason, such as surgery or illness, call your doctor. SYMLIN should be restarted as described in “How should I use SYMLIN?”**

When should I not use SYMLIN?

Do not use SYMLIN if:

- your blood sugar is too low.
- you do not plan to eat. Do not inject SYMLIN if you skip a meal.
- you plan to eat a meal with less than 250 calories or 30 grams of carbohydrate.
- you are sick and can't eat your usual meal.
- you are having surgery or a medical test where you cannot eat.
- you are pregnant or breastfeeding and have not talked to your doctor.

Talk to your doctor if you have any of these conditions.

What should I avoid while taking SYMLIN?

- Do not drive or operate dangerous machinery until you know how SYMLIN affects your blood sugar. Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others. Discuss with your doctor what activities you should avoid.
- Alcohol may increase the risk of low blood sugar.
- **Your doctor will tell you which medicines you can take while using SYMLIN. Do not take other medicines that slow stomach emptying.**

Always have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon available to treat low blood sugar.

What are the possible side effects of SYMLIN?

Low blood sugar (hypoglycemia)

- **SYMLIN is used with insulin to lower your blood sugar, but your blood sugar may drop too low, especially if you have type 1 diabetes.** See “What is the most important information I should know about SYMLIN?”
- When starting SYMLIN, reduce your doses of insulin before meals as recommended by your doctor to reduce the chance of low blood sugar. You and your doctor should talk about a plan to treat low blood sugar. You should have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon with you at all times. Call your doctor if you have low blood sugar more often than normal or severe low blood sugar.

Your chance for low blood sugar is higher if you:

- do not reduce your insulin dose before meals at the beginning of SYMLIN treatment, as directed by your doctor.
- use more SYMLIN or insulin than prescribed by your doctor.
- change your insulin dose without checking your blood sugar.
- eat less food than your usual meal.
- are sick and cannot eat.
- are more active than usual.
- have a low blood sugar level before eating.
- drink alcohol.

Nausea: Nausea is the most common side effect with SYMLIN. Mild nausea is more likely during the first weeks after starting SYMLIN and usually does not last long. It is very important to start SYMLIN at a low dose and increase it as directed by your doctor. See “How should I use SYMLIN?” If nausea continues or bothers you, call your doctor right away.

Other Side Effects: SYMLIN also may cause the following side effects: decreased appetite, vomiting, stomach pain, tiredness, dizziness, or indigestion.

SYMLIN also can cause reactions at the injection site including redness, minor bruising, or pain. Follow the directions under “How should I use SYMLIN?” to reduce the chance of an injection site reaction.

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all the side effects with SYMLIN. Ask your doctor or pharmacist for more information.

How should I store SYMLIN?

- Store SYMLIN vials in the refrigerator until you open them.
- Opened vials can be refrigerated or kept at room temperature for up to 28 days. Any opened vial should be thrown away after 28 days, even if it still has medicine in it.
- Vials should not be left at above room temperature (77°F/25°C). Throw away any vial that is:
 - out-of-date.
 - has been frozen.
 - left at above room temperature (77°F/25°C).
 - left at room temperature for more than 28 days.

Please call SYMLIN Customer Service with any questions (see telephone number below).

- **Keep SYMLIN and all medicines out of the reach of children.**

General information about the safe and effective use of SYMLIN

Medicines are sometimes prescribed for conditions other than those described in a Medication Guide. Do not use SYMLIN for a condition for which it was not prescribed. Do not give SYMLIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SYMLIN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about SYMLIN that is written for health professionals.

More information on SYMLIN can be found at <http://www.symlin.com>.

SYMLIN Customer Service is available 24 hours a day at 1-800-349-8919.

What are the ingredients in SYMLIN?

Active ingredient: pramlintide acetate

Inactive ingredients: metacresol, D-mannitol, acetic acid, and sodium acetate.

This Medication Guide is approved by the U.S. Food and Drug Administration.

Literature issued June 2005.

Manufactured for Amylin Pharmaceuticals, Inc.

San Diego CA 92121, USA

1-800-349-8919

<http://www.symlin.com>

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Insulin



Simplifying one of the most misunderstood medications of all time.

By [Wil Dubois](#)

It's clearer than water from an alpine mountain spring. It's as expensive as French perfume. It's nearly 100 years old. It's been blessed, cursed, feared, and loved. Virtually all animals have it, or something very much like it. Horses have it. Dogs have it. Mice have it. Fish have it. So too do earthworms, fruit flies, and mosquitos.

It's [insulin](#).

In the Body

From the perspective of biology, insulin is the elixir of the Fountain of Life. OK, well, technically it's a peptide hormone, meaning that it's a functional protein—a protein engineered by nature to carry out a specific task. If you want to get even more technical about it, insulin is composed of 51 amino acids and has a molecular weight of 5808.

In "normal" people and critters, insulin is produced by the body's [pancreas](#). The hormone's job is to guide glucose molecules from the blood stream into individual cells, earning it the title of a "transport hormone." Insulin is a navigator, hunting guide, and traffic cop all rolled into one. If your body fails to produce insulin you have [type 1 diabetes](#), and your blood sugar *rapidly* skyrockets with potentially deadly effect. If your body produces insulin—but not enough for its needs because of insulin resistance—you have [type 2 diabetes](#), and your blood sugar *slowly* skyrockets, but still with potentially deadly effect.

In the Bottle

From the perspective of diabetes therapy, insulin is the ultimate medicine. It always works. It gets along well with other [medications](#). There is no maximum safe amount. It has virtually no side effects—it won't make you cough, ache, burp, or have diarrhea. It's infinitely scalable. It's simple, safe, and natural.

Insulin has a long track record, too. It was "discovered" and synthesized nearly a century ago by Dr. Frederick Banting and his assistant Charles Best working at the University of Toronto. Over the decades since, insulin has had a number of makeovers, but it's the same basic molecule. It was originally distilled from ground-up animal pancreases, generally from cows and pigs. In recent decades "human" insulin has been grown in massive production plants, using either yeast or *E.coli* bacteria.

It has come in a variety of "strengths," and over time various chemicals have been added to slow down its action or speed to it up. So while over the years it has featured different lights, bells, and whistles, it remains the same basic medicine.

But I don't want to talk about the body's insulin today. I want to talk about insulin in a bottle.

Who Needs Insulin?

Everyone, of course. But I guess you were asking which people with diabetes need insulin from a bottle. Actually, the answer is the same: everyone. Now all type 1's need insulin right out of the gate. I think most people know that. Our bodies don't make any at all and to stay alive we must import insulin from outside to keep the sugar in our blood in check. But what is less well known is that *virtually all* type 2s—in the fullness of time—will also need insulin from outside.

The reason for this is simple: Type 2 diabetes is a progressive disease. It gets worse and worse and worse over time. Pills will only go so far. Eventually, most type 2s who live long enough will need insulin. So, given the natural course of diabetes and the almost guaranteed need for insulin, why do so many people freak out about taking it? Well, it might be that taking insulin involves needles.

Why a Needle?

Insulin needs to be injected. Why? Why can't we have a pill? Well, remember that I told you that it's actually a protein? So if you put it in a pill, your stomach mistakes it for a T-bone steak and digests it. Trust me, pharma companies big and small are working night and day on a work-around to put insulin into a pill, but with no great success yet.

OK, why can't we have a patch? Well, remember that I told you insulin has an atomic weight of 5808? In plain English that means it has a very big butt. It's a huge mongo molecule. Too big, in fact, to fit through your skin. That's why nothing happens if you pour insulin onto your hands. But again, the friendly pharma folks are working on ways to stretch the skin to force the molecules in. But don't hold your breath. The I-patch is years away.

In the meantime, to get insulin through your skin and into your body without being digested, a needle is involved. That needle might be attached to an ol' fashioned insulin syringe, something called an [insulin pen](#), or to an insulin pump.

Insulin (Continued)

Syringes, Pens, and Pumps, Oh My!

I think everyone knows what a syringe is: It's a tube designed to hold a liquid, a plunger to draw the liquid into the tube and push it out again, and a needle to break the human skin to get the liquid where it needs to go. Once upon a time, only a few decades ago, syringes were glass and metal affairs that had to be boiled between uses, and needles were giant stainless steel harpoons that had to be sharpened on whetstones like knives. Now we have disposable plastic one-shot syringes with [high-tech needles](#) the size of a human eyelash. Syringes are the traditional way to deliver insulin, and are still commonly in use in the USA today.

In some parts of this country, and in most of the rest of the civilized world, the syringe has been replaced by the pen. An insulin pen is a fountain pen-sized multi-shot device with a tiny screw cap needle on one end and a dial to set a dose on the other end. They come in both pre-filled disposable varieties, and in sturdy metal beauties that can be refilled.

Lastly, an [insulin pump](#) is an alternative way to get insulin into the body. It's a high-tech computerized device that automates some, but not all, of insulin delivery. Instead of one big shot, pumps continuously infuse small amounts of insulin into your body all of the time.

A Good Girl with a Bad Reputation

Now in all fairness, insulin cannot be said to be neither feminine nor masculine, but it's certainly one of the most misunderstood medications of all time. I say that because many people are terrified of going "on" insulin. Is it just the needle? After all, sticking yourself with a needle is arguably an unnatural (but nowadays painless) act.

No, fear of needles isn't the whole story. Because if we look at other injectable diabetes medications like [Byetta](#) and [Victoza](#), there's very little resistance from dFolk to taking these meds, which also require needles. So, does the lure of weight loss overcome the fear of needles, or is there something else going on?

How did insulin get such a bum rep?

The answer: Stupid doctors. For decades many docs tried to control their patients' behavior by using fear. They'd hold up the vial and syringe like a baseball bat: "You'd better do what I tell you or I'll have to put you on the needle."

(A rather short-sighted motivational technique given that the natural history of diabetes shows us nearly everyone with diabetes will end up on insulin at some point.)

Thus, used as a threat, insulin became the *de facto* medication of last resort. Often the elixir of life was delayed too long. Historically, by the time many type 2s were started on insulin, complications had already set in. Families remembered that grandma was put on insulin and then went blind. Families remembered that grandpa was put on insulin and then his feet were cut off. Avoid insulin: that stuff will kill you!

It was the combination of these three factors that ended up giving insulin a bad rep that the best PR firm in the world would have a hard time overcoming. First, doctors in the past used insulin as a threat, creating an atmosphere of fear around the best diabetes

medicine in the pharmacy. Second, in most cases, it was started far too late in the disease process, after the damage was already done. If grandma and grandpa had been started on insulin a decade earlier they'd be alive and kicking (with both feet) today. Third, type 2 diabetes is commonly inter-generational: And families have pretty good memories. More about that last one in a minute.

Insulin Today

Luckily, the vast majority of the medical community has "gotten with the program." Insulin isn't held over patient's heads as a threat anymore. It's started in a timely manner now. In some practices it's viewed as a medicine of first resort, not of last resort. Most patients are told that insulin is in the cards from the very day they are diagnosed. The natural progression of diabetes is carefully laid out so that no fear or self-blame need exist down the road.

Still, family lore,... that's not so easily changed. The mythologies, memories, misgivings and outright fear of insulin generated by the dark history of insulin's use will take much more time to cure.

But hopefully not the next 100 years of insulin's history.

Wil Dubois is the author of four multi-award-winning books about diabetes. He is a PWD type 1, and is the diabetes coordinator for a rural non-profit clinic. Visit his blog, [LifeAfterDX](#).

TYPES OF INSULIN AND HOW THEY WORK

There are many types of insulin. Some work slowly and some quickly.

Slower or long-acting insulin is also called *basal insulin*. Basal insulins deliver a steady supply of insulin that helps control blood sugar levels over time.

Fast-acting insulin is also called *bolus insulin*. Bolus is a fancy word for “extra.”

Times when your body may need some fast-acting (extra) insulin include when you are:

- Sick
- Under stress
- About to eat a meal
- Having a high blood sugar problem

The table below will help you understand how many commonly used insulins work. Your doctor or nurse will help you choose the insulin that's right for you.

Types of Insulin	Common Insulin Names	When It's usually taken	How soon it starts working*	When It's working the most*	How long it lasts*
Fast-acting Insulin	NovoLog Humalog Apidra	Right before a meal	15 minutes	30 to 90 minutes	3 to 5 hours
Long-acting Insulin	Lantus Levemir	30 minutes before the evening meal or at bedtime	1 hour	Steady over time	Up to 24 hours
Short-acting Insulin (also called regular insulin)	Novolin R Humulin R	30 minutes before a meal	30 to 60 minutes	2 to 4 hours	5 to 8 hours
Medium-acting (Intermediate-acting) (NPH) Insulin	Humulin N Novolin N	30 minutes before breakfast or at bedtime	1 to 3 hours	8 hours	10 to 16 hours
Premixed mixture of fast-acting and medium-acting (NPH) Insulin	Humalog Mix 75/25 Humalog Mix 50/50 NovoLog 70/30	Before breakfast and/or before the evening meal	5 to 15 minutes	Varies	10 to 16 hours
Premixed mixture of short-acting (regular) and medium-acting (NPH) Insulin	Humulin 70/30 Novolin 70/30 Humulin 50/50	30 minutes before breakfast and/or before the evening meal	30 to 60 minutes	Varies	10 to 16 hours

*Insulin times may vary. Talk to your doctor for more information. Ref: http://diabetes.niddk.nih.gov/dm/pubs/medicines_ez/insert_C.asp

NovoLog (insulin aspart injection)

Patient Information

NovoLog(NŌ-vō-log)
(insulin aspart injection)

Do not share your NovoLog FlexPen®, NovoLog®FlexTouch, PenFillcartridge or PenFill® cartridge compatible insulin delivery device with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is NovoLog?

- NovoLog ®is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not take NovoLog

®
?

Do not take NovoLog® if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to NovoLog
- or any of the ingredients in NovoLog®

.

Before taking NovoLog®

, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

, talk to your healthcare provider about low blood sugar and how to manage it.

Read the Instructions for Use that come with your NovoLog®

- Take NovoLog exactly as your healthcare provider tells you to.

.

NovoLog ®starts acting fast. You should eat a meal within 5 to 10 minutes after you take your dose of NovoLog®

.

- Know the type and strength of insulin you take.

Do not change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.

.

Check your blood sugar levels.

Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

.

Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.

While taking NovoLog®

Do Not:

- Drive or operate heavy machinery, until you know how NovoLog® affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of NovoLog®?

NovoLog® may cause serious side effects that can lead to death, including: Low blood sugar (hypoglycemia).

Signs and symptoms that may indicate low blood sugar include:

- dizziness or light-headedness
- blurred vision
- anxiety, irritability, or mood changes
- sweating
- slurred speech
- hunger
- confusion
- shakiness
- headache
- fast heart beat

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Other common side effects of NovoLog® may include:

- low potassium in your blood (hypokalemia), reactions at the injection site, itching, rash, serious allergic reactions (whole body reactions), skin thickening or pits at the injection site (lipodystrophy), weight gain, and swelling of your hands and feet.

Get emergency medical help if you have: trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of NovoLog®

. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of NovoLog®

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

You can ask your pharmacist or healthcare provider for information about NovoLog®

that is written for health professionals. Do not use NovoLog® for a condition for which it was not prescribed. Do not give NovoLog® to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in NovoLog®?

Active Ingredient: insulin aspart

Inactive Ingredients: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride and water for injection

Manufactured by:

Novo Nordisk A/S; DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 03/2017

NovoLog® is a registered trademark of Novo Nordisk A/S.

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NovoLog® (insulin aspart injection)

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: March 2017

NovoLog® is a registered trademark of Novo Nordisk A/S.

Patent Information: <http://novonordisk-us.com/patients/products/product-patents.html>

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about NovoLog® contact:

Novo Nordisk Inc.

800 Scudders Mill Road

Plainsboro, New Jersey 08536

1-800-727-6500

www.novonordisk-us.com

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USA17INP00949 4/2017

Instructions for Use

NovoLog® (NŌ-vō-log)

(insulin aspart injection)

10 mL vial (100 Units/mL, U-100)

Read this Instructions for Use before you start taking NovoLog® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Supplies you will need

to give your NovoLog

®

injection:

- 10 mL NovoLog

®

vial

- insulin syringe and needle
- alcohol swab

Preparing your NovoLog

®

dose:

- Wash your hands with soap and water.

• Before you start to prepare your injection, check the NovoLog® label to make sure that you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.

- NovoLog® should look clear and colorless.

Do not use NovoLog® if it is thick, cloudy, or is colored.

•

Do not

use NovoLog® past the expiration date printed on the label.

Step 1:

Pull off the tamper

resistant cap (See Figure A).

Step 2:

Wipe the rubber stopper with an alcohol swab (See Figure B).
(Figure A Figure B)

Step 3:

Hold the syringe with the needle pointing up. Pull down on the plunger until the black tip reaches the line for the number of units for your prescribed dose (See Figure C).
(Figure C)

Step 4:

Push the needle through the rubber stopper of the NovoLog® vial (See Figure D).
(Figure D)

Step 5:

Push the plunger all the way in. This puts air into the NovoLog® vial (See Figure E).
(Figure E)

Step 6:

Turn the NovoLog® vial and syringe upside down and slowly pull the plunger down until the black tip is a few units past the line for your dose .

(Figure F)

- If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top (See Figure G).

Step 7:

Slowly push the plunger up until the black tip reaches the line for your NovoLog® dose (See Figure H).

Step 8:

Check the syringe to make sure you have the right dose of NovoLog®.

Step 9:

Pull the syringe out of the vial's rubber stopper (See Figure I).

Giving your Injection: • Inject your NovoLog® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting. • NovoLog® can be injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms, infused in an insulin pump, or given through a needle in your arm (intravenously) by your healthcare provider.

- If you inject NovoLog®, change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

- If you use NovoLog® in an insulin pump, you should change your insertion site every 3 days. The insulin in the reservoir should be changed at least every 6 days even if you have not used all of the insulin.

- If you use NovoLog® in an insulin pump, see your insulin pump manual for instructions or talk to your healthcare provider.

- NPH insulin is the only type of insulin that can be mixed with NovoLog®

Do not mix NovoLog® with any other type of insulin. NovoLog® should only be mixed with NPH insulin if it is going to be injected right away under your skin (subcutaneously).

- NovoLog® should be drawn up into the syringe before you draw up your NPH insulin.
- Talk to your healthcare provider if you are not sure about the right way to mix NovoLog® and NPH insulin.

Step 10:

Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose. (Figure J) Back Front

Step 11:

Insert the needle into your skin. Push down on the plunger to inject your dose (See Figure K). Needle should remain in the skin for at least 6 seconds to make sure you have injected all the insulin. (Figure K)

Step 12:

Pull the needle out of your skin. After that, you may see a drop of NovoLog® at the needle tip. This is normal and does not affect the dose you just received (See Figure L).

- If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab.

Do not rub the area.

(Figure L)

After your injection:

Do not recap the needle. Recapping the needle can lead to a needle stick injury.

- Throw away empty insulin vials, used syringes, and needles in a sharps container or some type of hard plastic or metal container with a screw on cap such as a detergent bottle or empty coffee can.

Check with your healthcare provider about the right way to throw away the container. There may be local or state laws about how to throw away used syringes and needles. Do not throw away used syringes and needles in household trash or recycling bins.

How should I store NovoLog®?

Do not freeze NovoLog® so not use NovoLog® if it has been frozen.

- Keep NovoLog® away from heat or light.
- Store opened and unopened NovoLog® vials in the refrigerator at 36°F to 46°F (2°C to 8°C).
Opened NovoLog® vials can also be stored out of the refrigerator below 86°F (30°C).
- Unopened vials may be used until the expiration date printed on the label, if they are kept in the refrigerator.

- Opened NovoLog®

vials should be thrown away after 28 days, even if they still have insulin left in them.

General information about the safe and effective use of NovoLog® • Always use a new syringe and needle for each injection.

- Do not share syringes or needles.
- Keep NovoLog® vials, syringes, and needles out of the reach of children. Tamperresistant cap Rubber Stopper (Undercap)

Vial8 NovoLog® (insulin aspart injection)

Giving the injection. Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.

NovoLog® can be injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs (thighs), or upper arms. For each injection, change (rotate) your injection site within the area of skin that you use. Do not use the same injection site for each injection.

I.

Insert the needle into your skin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see

diagram I). Be careful only to push the button when injecting. Turning the dose selector will not inject insulin.

J.

Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram J). This will make sure that the full dose has been given.

J

You may see a drop of insulin at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger.

Do not rub the area. After the injection

Do not recap the needle.

Recapping can lead to a needle stick injury. Remove the needle from the NovoLog® FlexPen after each injection and dispose of it. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

If you do not have a sharps container, carefully slip the needle into the outer needle cap. Safely remove the needle and throw it away as soon as you can.

-

Put your used NovoLog® FlexPen® and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.

-

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- o

made of a heavy-duty plastic

- o

WWH has free Home Sharps Containers for used lancet and pen needle containment and proper storage.

-

The NovoLog® FlexPen® prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

-

Put the pen cap on the NovoLog® FlexPen® and store the NovoLog® FlexPen® without the needle attached (see diagram K). Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

How should I store NovoLog® FlexPen® ?

Store unused NovoLog® FlexPen® in the refrigerator at 36°F to 46°F (2°C to 8°C).•

Store the FlexPen® you are currently using out of the refrigerator below 86°F (30°C) for up to 28 days.

Do not freeze NovoLog®

-

Do not use NovoLog® if it has been frozen.

-

Keep NovoLog® away from heat or light. Instructions For Use NovoLog® FlexPen® Introduction

Please read the following instructions carefully before using your NovoLog® FlexPen®.

Do not share your NovoLog® FlexPen® with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them. NovoLog® FlexPen is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit.

NovoLog® FlexPen® is designed to be used with NovoFine® NovoFine® Plus or NovoTwist® needles.

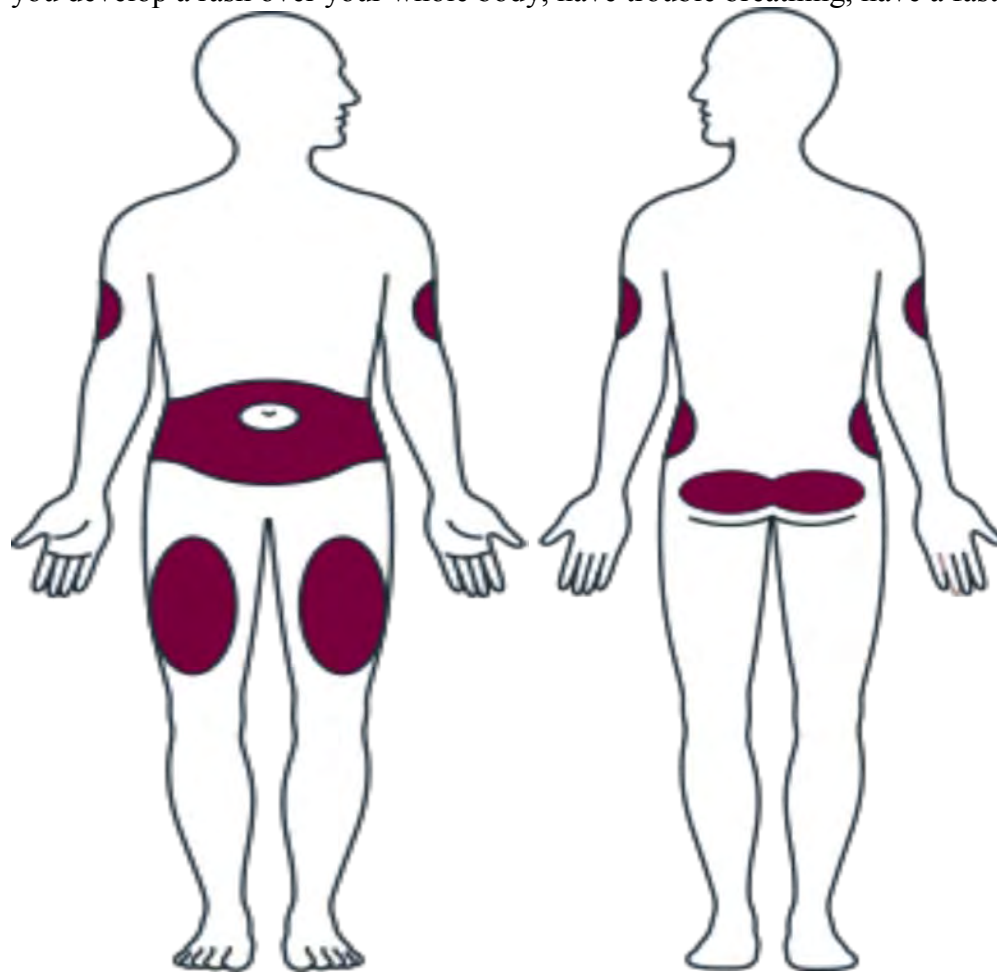
NovoLog® FlexPen® should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog® FlexPen® the right way.

Where to inject Humalog U-100

Humalog may be injected under the skin of the stomach area, back of upper arms, upper legs, or buttocks (see diagram). Never inject Humalog into a muscle or vein. Work with your healthcare team to determine the most appropriate injection sites.

Be sure to use a different injection site each time and do not overuse any site. Severe life-threatening allergic reactions (whole-body reactions) can happen. Get medical help right away if

you develop a rash over your whole body, have trouble breathing, have a fast heartbeat or are



Reactions at the injection site (local allergic reaction) such as redness, swelling, and itching can happen. If you keep having skin reactions or they are serious, talk to your doctor. Do not inject insulin into a skin area that is red, swollen, or itchy.

Storage and disposal for Humalog U-100 KwikPen

Unopened Humalog should be stored in a refrigerator and can be used until the expiration date on the carton or label.

Humalog should be stored away from light and heat.

Do not use insulin if it has been frozen.

Opened cartridges or prefilled pens should be kept at room temperature.

Prefilled pens and cartridges should be thrown away 28 days after the first use even if there is insulin remaining.

Dispose of needles and pens as directed by your doctor.



Other ways to take Humalog U-100

There are other ways to take Humalog besides Humalog KwikPen. The choices currently available are vial and syringe, Humalog Junior KwikPen, HumaPen® LUXURA® HD, and an insulin pump. To decide which way is right for you, ask your doctor about these options and discuss the pros and cons.

[Click here to learn how to use a vial and syringe for Humalog U-100.](#)

[NEW TO TYPE 1 DIABETES?](#)

Storage and disposal for vials

Store all unopened (unused) vials in the original carton in a refrigerator. Do not freeze.

Unopened, refrigerated vials can be kept until expiration date.

After first use (opened), store vial in the refrigerator (not the freezer) or, if necessary, at room temperature below 86°F (30°C). Do not use if vial has been frozen.

Throw away open vials 28 days after first use, even if there is insulin left in the vial.

Do not use after the expiration date printed on the carton and label.

Protect from direct heat and light.

Safely dispose of needles and syringes as directed by your doctor.

For full storage and disposal information, please see the Patient Information leaflet that comes with your insulin.

Disposal of needles and syringes

Place all needles and syringes in a sharps disposal container immediately after they have been used.

- Never place loose needles in any trash can or recycling bin and never flush them down the toilet
- Carry a small, travel-size sharps disposal container when leaving home

Dispose of the sharps container according to community guidelines.

- Do not reuse sharps containers

For information about disposal of syringes and needles, visit the US Food and Drug Administration website at [fda.gov/safesharpsdisposal](https://www.fda.gov/safesharpsdisposal) or call [1-888-INFO-FDA \(1-888-463-6332\)](tel:1-888-INFO-FDA).

Humalog Junior KwikPen and HumaPen® LUXURA® HD

Primarily for people with type 1 diabetes who need small, precise doses, Humalog Junior KwikPen and HumaPen LUXURA HD allow dosing in half-units starting at 0.5 units.



[More information about Humalog Junior KwikPen](#)



HumaPen
LUXURA

[More information about HumaPen LUXURA HD](#)

Why use a pump?

For some people, an insulin pump can help improve diabetes management and make it more flexible. A pump may be a good option if any of these apply:

- You regularly test your blood sugar
- You are active and have an inconsistent meal and physical activity schedule
- You have demonstrated the ability to manage your diabetes but don't want to draw attention to it



Have your healthcare team discuss the pros and cons of external insulin pumps with you. They can help you decide whether taking Humalog with an external insulin pump is right for you.

Select Safety Information

Failure of your insulin pump or infusion set or degradation of the insulin in the pump can cause hyperglycemia and ketoacidosis. Always carry an alternative form of insulin administration in case of pump failure.

When used in a pump, do not mix Humalog U-100 with any other insulin or liquid. Do not use Humalog Mix75/25, Humalog Mix50/50, or Humalog U-200 in a pump.

An insulin pump is another way to deliver Humalog U-100 to your body. The insulin pump stores Humalog inside it and has a small, bendable, plastic tube attached at one end. This tube goes into the skin through a small needle. Once the tube is set in place, the needle is removed. To deliver the amount of insulin needed, a button on the pump is pushed. The pump is small enough to be worn on a belt or kept in a pocket.

Frequently Asked Questions

How long does Humalog KwikPen last once I've begun using it?

You will need to discard your Humalog KwikPen after 28 days in use, even if insulin remains.

Will there be insulin left in my pen when it's time to discard it?

KwikPen is designed to deliver a total of 300 units of insulin. The cartridge contains an additional small amount of insulin that cannot be delivered, so you will see a small amount of insulin left in your pen when it's time to discard it. **Remember: Never withdraw Humalog from the pen using a syringe. It could result in an overdose causing severe low blood sugar, which may put your life in danger.**

Must I prime my pen before using it?

Yes, you need to prime your pen. If you do not prime, you may get too much or too little insulin. You will turn the dose knob to 2 units. Hold your pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top. Continue holding your pen with the needle pointing up. Push the dose knob in until it stops and "0" is seen in the dose window. Hold the dose knob in and count to 5 slowly. You should see insulin at the tip of the needle.

Where do I inject U-100 insulin?

Rotate between typical injection sites, such as the abdomen, buttocks, upper legs, or upper arms. Never inject Humalog into a muscle or vein. [View the demonstration video for more information.](#)

What should I do if the dose knob is hard to push?

- Pushing the dose knob more slowly will make it easier to inject
- Your needle may be blocked. Put on a new needle and prime the pen
- You may have dust, food, or liquid inside the pen. Throw the pen away and get a new pen

Do not withdraw insulin from the pen with a syringe. If the dose knob is still difficult to push, contact your pharmacy or The Lilly Answers Center at [1-800-LillyRx](tel:1-800-LillyRx) (1-800-545-5979). [View the demonstration video for more information.](#)

What are the potential side effects for U-100?

Low blood sugar is the most common side effect. Other possible side effects include severe life-threatening allergic reactions and reactions at the injection site. Please see [Important Safety Information](#) for additional side effects. Ask your healthcare provider for more information or for medical advice.

What should I do if I am experiencing any side effects?

If you are experiencing any side effects, please contact your doctor. You may also report side effects to the Food and Drug Administration at [1-800-FDA-1088](tel:1-800-FDA-1088) or contact The Lilly Answers Center at [1-800-LillyRx](tel:1-800-LillyRx) ([1-800-545-5979](tel:1-800-545-5979)).

Why use a pump?

For some people, an insulin pump can help improve diabetes management and make it more flexible. A pump may be a good option if any of these apply:

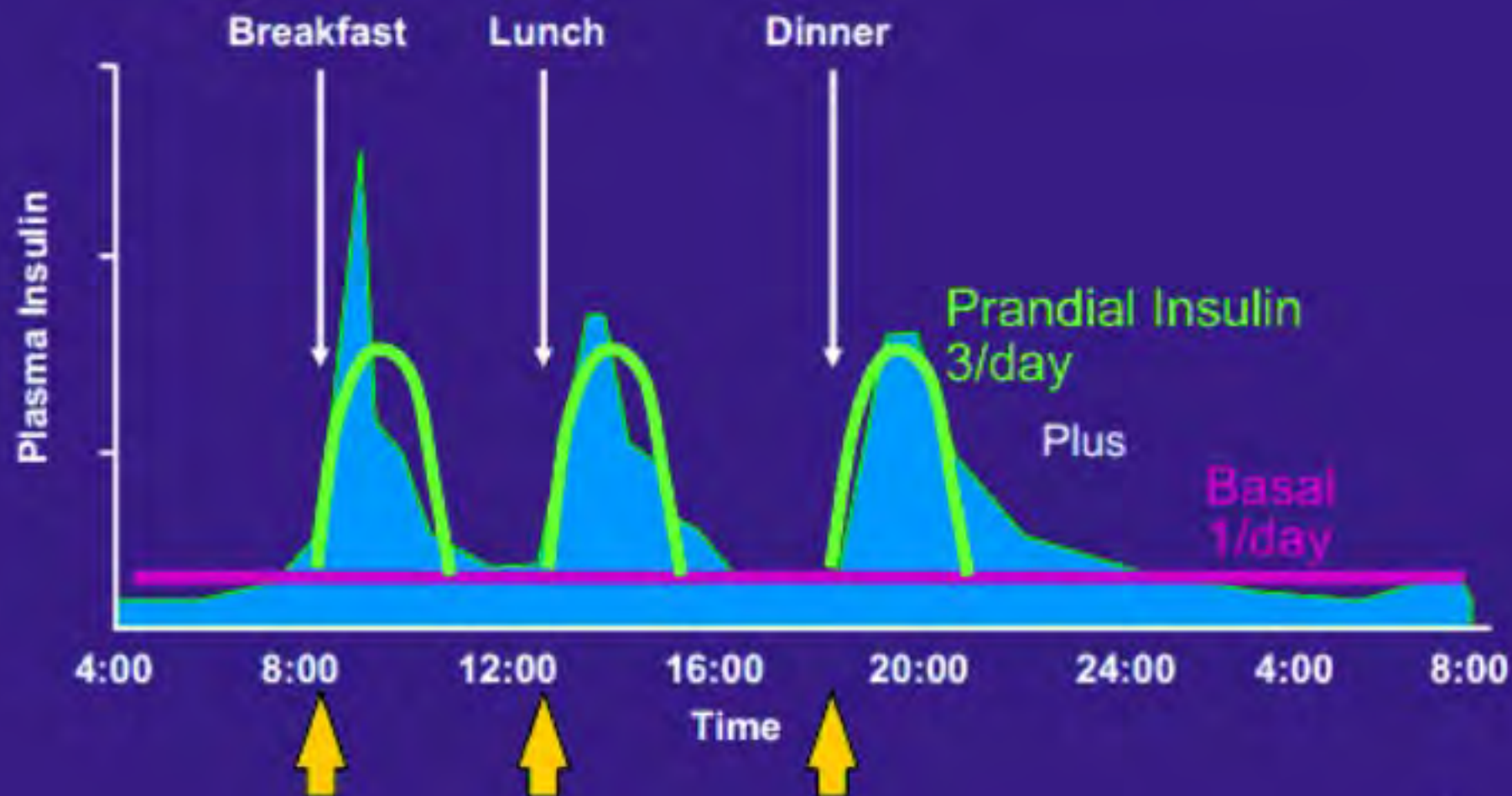
- You regularly test your blood sugar
- You are active and have an inconsistent meal and physical activity schedule
- You have demonstrated the ability to manage your diabetes but don't want to draw attention to it

Ask your doctor to discuss the pros and cons of external insulin pumps with you. He or she can help you decide whether taking Humalog with an external insulin pump is right for you.

What if I need additional help getting started with Humalog U-100?

Humalog offers a health mentor to help you get started on mealtime insulin therapy with your best foot forward. This phone-based support program provides eligible patients with live phone calls from a trained health mentor. Your health mentor can help you get started with Humalog, explain Humalog in more detail, and answer any questions you might have. To find out if you're eligible to speak with a health mentor, call [\(855\) 232-1059](tel:855-232-1059).

Mimicking Physiology: Basal and Prandial Insulin



Types of Insulin

Rapid-acting:

- Inhaled human insulin

Rapid-acting analogs:

- Aspart, Glulisine, Lispro (U-100 or U-200)

Short-acting insulin: Regular (soluble)

Intermediate-acting insulin: NPH

Human insulin 70/30:

- Premix NPH/regular

Premixed Analogs:

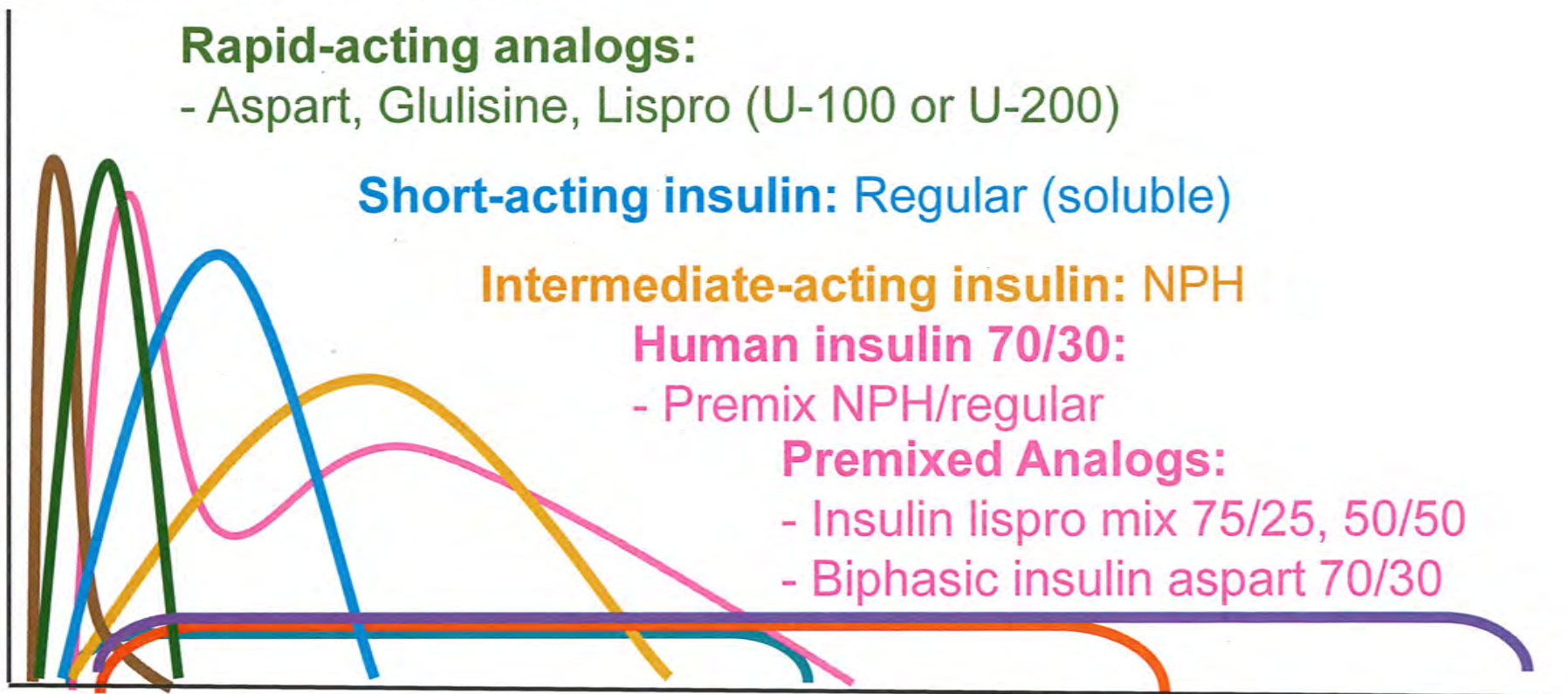
- Insulin lispro mix 75/25, 50/50
- Biphasic insulin aspart 70/30

Long-acting insulin:

Detemir, Glargine

Glargine U-300

Degludec U-100 or U-200



Instructions for Use
ADMELOG® SoloStar® (ad-mah-log)
(insulin lispro injection) for subcutaneous use
3 mL disposable prefilled pen (100 Units/mL, U-100)

Read this first

Do not share your ADMELOG SoloStar pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

ADMELOG SoloStar should not be used by people who are blind or have severe vision problems without the help of a person who has good eyesight and who is trained to use the ADMELOG SoloStar the right way.

ADMELOG SoloStar is a disposable prefilled pen used to inject ADMELOG. Each ADMELOG SoloStar has 300 units of insulin which can be used for multiple injections. You can select doses from 1 to 80 units in steps of 1 unit. The pen plunger moves with each dose. The plunger will only move to the end of the cartridge when 300 units of insulin have been given.

Important information

- **Do not** use your pen if it is damaged or if you are not sure that it is working properly.
- **Do not** use a syringe to remove insulin from your pen.
- **Do not reuse needles.** If you do, you might get the wrong dose of ADMELOG and/or increase the chance of getting an infection.
- Always perform a safety test (see **Step 3**).
- Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject

- Talk with your healthcare provider about how to inject before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get too much or too little insulin.

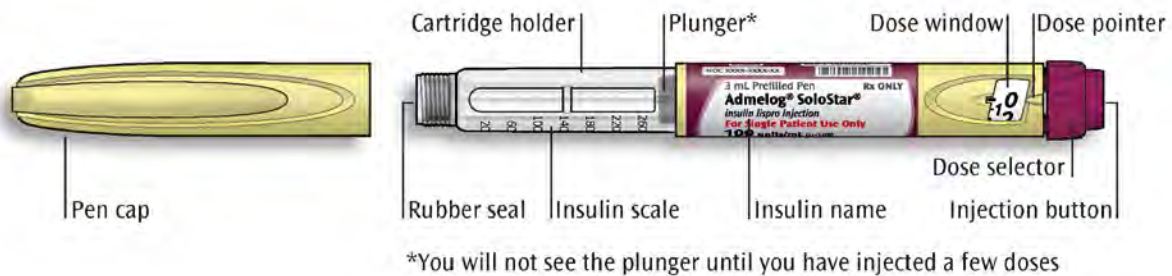
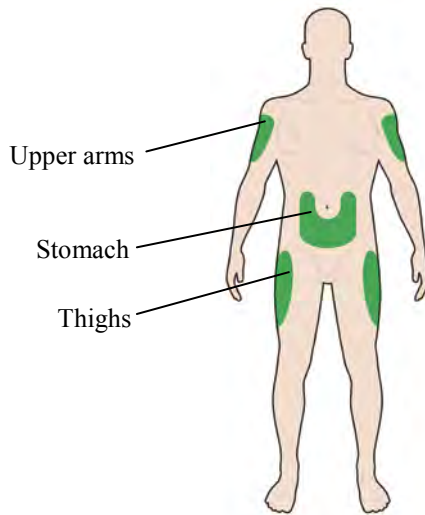
Need help?

If you have any questions about your pen or about diabetes, ask your healthcare provider, or go to **www.Admelog.com** or call sanofi-aventis at **1-800-633-1610**.

Extra items you will need:

- a new sterile needle (see **Step 2**).
- an alcohol swab.
- a puncture-resistant container for used needles and pens. (See **“Throwing your pen away”**).

Places to inject



Step 1: Check your pen

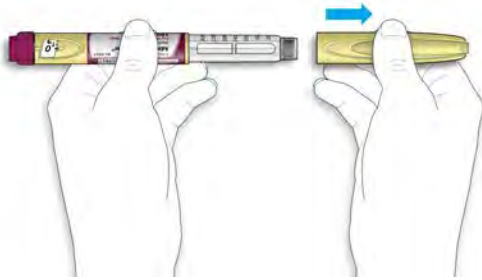
Take a new pen out of the refrigerator at least **1** hour before you inject. Cold insulin is more painful to inject.

1A Check the name and expiration date on the label of your pen.

- Make sure you have the correct insulin.
- **Do not** use your pen after the expiration date.



1B Pull off the pen cap.

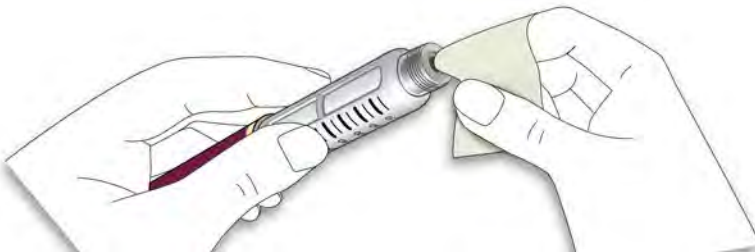


1C Check that the insulin is clear.

- **Do not** use the pen if the insulin looks cloudy, colored or contains particles.



1D Wipe the rubber seal with an alcohol swab.



If you have other injector pens:

- Making sure you have the correct medicine is especially important if you have other injector pens.

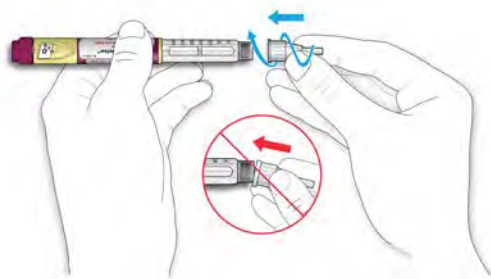
Step 2: Attach a new needle

- **Do not** reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination, and infection.
- Only use needles* that are compatible for use with ADMELOG SoloStar, e.g. needles from BD (such as BD Ultra-Fine®), Ypsomed (such as Clickfine®), Owen Mumford (such as Unifine® Pentips®).

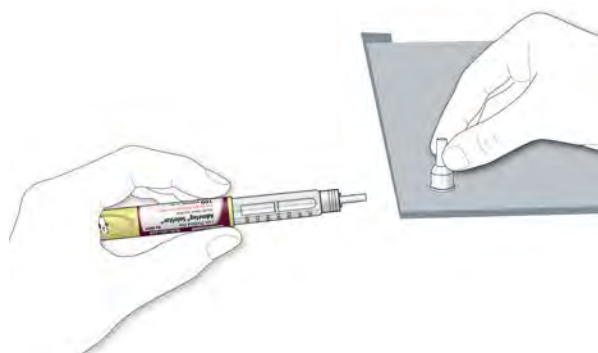
2A Take a new needle and peel off the protective seal.



2B Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



2C Pull off the outer needle cap. Keep this for later.



2D Pull off the inner needle cap and throw away.



Handling needles:

- Take care when handling needles to prevent needle-stick injury and cross-infection.

Step 3: Do a safety test

Always do a safety test before each injection to:

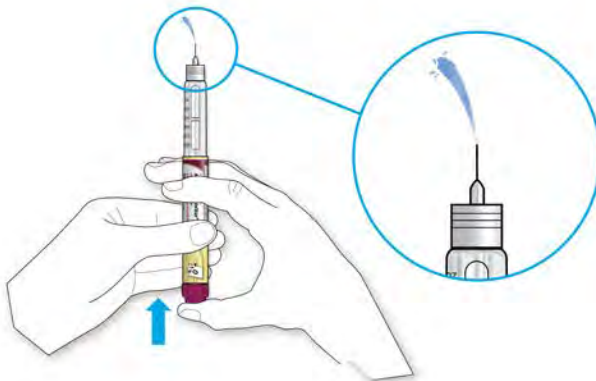
- Check your pen and the needle to make sure they are working properly.
- Make sure that you get the correct insulin dose.

3A Select 2 units by turning the dose selector until the dose pointer is at the 2 mark.



3B Press the injection button all the way in.

- When insulin comes out of the needle tip, your pen is working correctly.



If no insulin appears:

- You may need to repeat this step up to 3 times before seeing insulin.
- If no insulin comes out after the third time, the needle may be blocked. If this happens:
 - change the needle (see **Step 6** and **Step 2**),
 - then repeat the safety test (**Step 3**).
- **Do not** use your pen if there is still no insulin coming out of the needle tip. Use a new pen.
- **Do not** use a syringe to remove insulin from your pen.

If you see air bubbles:

- You may see air bubbles in the insulin. This is normal, they will not harm you.

Step 4: Select the dose

Do not select a dose or press the injection button without a needle attached. This may damage your pen.

4A Make sure a needle is attached and the dose is set to '0'.



4B Turn the dose selector until the dose pointer lines up with your dose.

- If you turn past your dose, you can turn back down.
- If there are not enough units left in your pen for your dose, the dose selector will stop at the number of units left.
- If you cannot select your full prescribed dose, use a new pen or inject the remaining units and use a new pen to complete your dose.



How to read the dose window

Even numbers are shown in line with dose pointer.



20 units selected

Odd numbers are shown as a line between even numbers.



21 units selected

Units of insulin in your pen:

- Your pen contains a total of **300** units of insulin. You can select doses from **1** to **80** units in steps of **1** unit. Each pen contains more than 1 dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale.

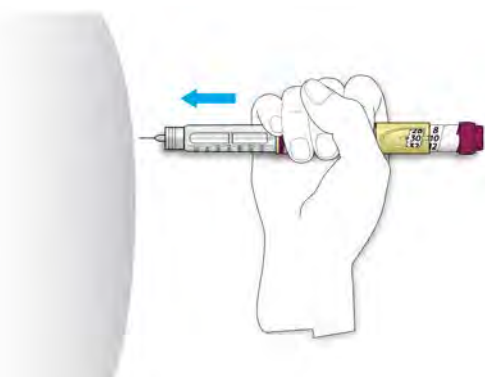
Step 5: Inject your dose

If you find it hard to press the injection button in, **do not** force it as this may break your pen. See the section below for help.

5A Choose a place to inject as shown in the picture above.

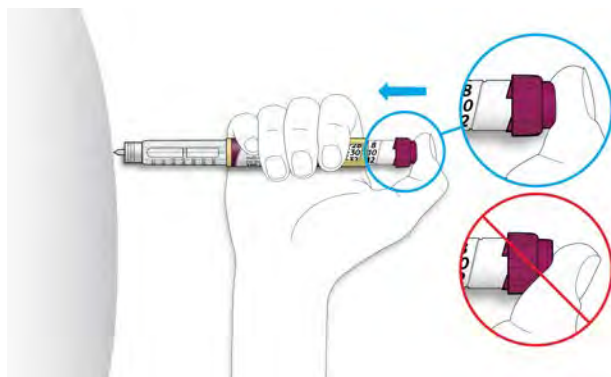
5B Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



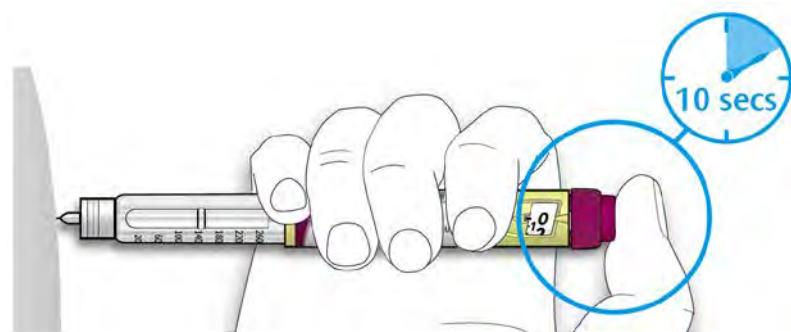
5C Place your thumb on the injection button. Then press all the way in and hold.

- **Do not** press at an angle. Your thumb could block the dose selector from turning.



5D Keep the injection button held in and when you see "0" in the dose window, slowly count to 10.

- This will make sure you get your full dose.



5E After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin.

If you find it hard to press the button in:

- Change the needle (see **Step 6** and **Step 2**) then do a safety test (see **Step 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove insulin from your pen.

Step 6: Remove the needle

- Take care when handling needles to prevent needle-stick injury and cross-infection.
- **Do not** put the inner needle cap back on.

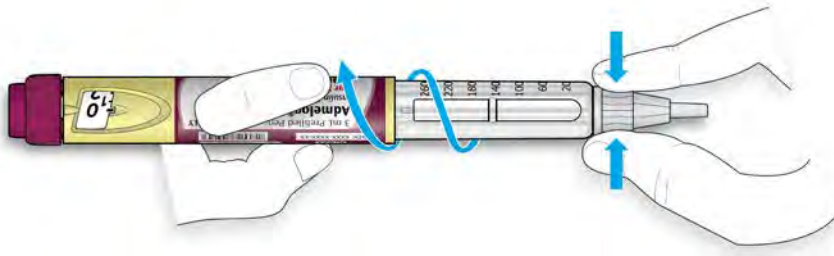
6A Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap. Then push firmly on.

- The needle can puncture the cap if it is recapped at an angle.



6B Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.

- Try again if the needle does not come off the first time.

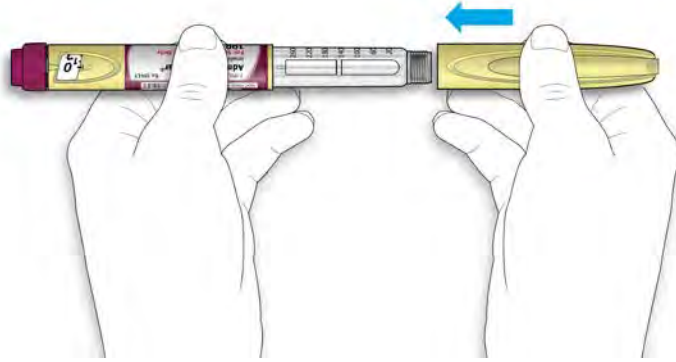


6C Throw away the used needle in a puncture-resistant container (see “Throwing your pen away” at the end of this Instructions for Use).



6D Put your pen cap back on.

- Do not put the pen back in the refrigerator.



How to store your pen

Before first use

- Keep new pens in the refrigerator between **36°F to 46°F (2°C to 8°C)**.
- **Do not** freeze. **Do not** use ADMELOG if it has been frozen.

After first use

- Keep your pen at room temperature **below 86°F (30°C)**.
- Keep your pen away from heat or light.
- Store your pen with the pen cap on.
- **Do not** put your pen back in the refrigerator.
- **Do not** store your pen with the needle attached.
- **Keep out of the reach of children.**
- Only use your pen for **up to 28 days** after its first use. Throw away the ADMELOG SoloStar pen you are using after 28 day, even if it still has insulin left in it.

How to care for your pen

Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- If you think that your pen may be damaged, **do not** try to fix it. Use a new one.

Protect your pen from dust and dirt

- You can clean the outside of your pen by wiping it with a damp cloth (water only). **Do not** soak, wash or lubricate your pen. This may damage it.

Throwing your pen away

- Put the used ADMELOG SoloStar pen in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the ADMELOG SoloStar pen in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and

- properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Approved: December 2017

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TRESIBA[®]

insulin degludec injection 100 U/mL, 200 U/mL

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRESIBA[®] safely and effectively. See full prescribing information for TRESIBA[®].

TRESIBA[®] (insulin degludec injection), for subcutaneous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Dosage and Administration (2)

03/2018

INDICATIONS AND USAGE

TRESIBA[®] is a long-acting human insulin analog indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus (1).

Limitations of Use:

Not recommended for treating diabetic ketoacidosis.

Not recommended for pediatric patients requiring less than 5 units of TRESIBA[®].

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for important administration instructions (2.1).
- Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- In adults, inject subcutaneously once daily at any time of day (2.2).
- In pediatric patients inject subcutaneously once daily at the same time every day (2.2).
- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal (2.2).
- The recommended days between dose increases are 3 to 4 days (2.2).
- See Full Prescribing Information for recommended starting dose in insulin naïve patients and patients already on insulin therapy (2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

TRESIBA[®] injection is available in the following package sizes:

- 100 units/mL (U-100): 3 mL FlexTouch[®] (3).
- 200 units/mL (U-200): 3 mL FlexTouch[®] (3).

CONTRAINDICATIONS

- During episodes of hypoglycemia (4).
- Hypersensitivity to TRESIBA[®] or one of its excipients (4).

WARNINGS AND PRECAUTIONS

- *Never share* a TRESIBA[®] FlexTouch[®] pen between patients, even if the needle is changed (5.1).

- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3, 5.4, 6.1).
- *Hypoglycemia due to medication errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer TRESIBA[®] into a syringe for administration as overdosage and severe hypoglycemia can result (5.4).
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TRESIBA[®], monitor and treat if indicated (5.5).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

ADVERSE REACTIONS

Adverse reactions commonly associated with TRESIBA[®] are:

- hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Drugs that may increase the risk of hypoglycemia:* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7).
- *Drugs that may decrease the blood glucose lowering effect:* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7).
- *Drugs that may increase or decrease the blood glucose lowering effect:* Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7).
- *Drugs that may blunt the signs and symptoms of hypoglycemia:* beta-blockers, clonidine, guanethidine, and reserpine (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2018

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

TRESIBA® is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

- Not recommended for the treatment of diabetic ketoacidosis.
- Not recommended for pediatric patients requiring less than 5 units of TRESIBA®.

2 DOSAGE AND ADMINISTRATION**2.1 Important Administration Instructions**

- Always check insulin labels before administration [see *Warnings and Precautions* (5.4)].
- Inspect visually for particulate matter and discoloration. Only use TRESIBA® if the solution appears clear and colorless.
- Inject TRESIBA® subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [see *Adverse Reactions* (6.1)].
- Use TRESIBA® with caution in patients with visual impairment that may rely on audible clicks to dial their dose.

- DO NOT administer TRESIBA® intravenously or in an insulin infusion pump.
- DO NOT dilute or mix TRESIBA® with any other insulin products or solutions.
- DO NOT transfer TRESIBA® from the TRESIBA® pen into a syringe for administration [see *Warnings and Precautions* (5.4)].

2.2 General Dosing Instructions

- TRESIBA® is available in 2 disposable prefilled pens:
 - TRESIBA® U-100 contains 300 units of TRESIBA® U-100. It delivers doses in 1 unit increments and can deliver up to 80 units in a single injection.
 - TRESIBA® U-200 contains 600 units of TRESIBA® U-200. It delivers doses in 2 unit increments and can deliver up to 160 units in a single injection.
- DO NOT perform dose conversion when using the TRESIBA® U-100 or U-200 pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.
- In adults, inject TRESIBA® subcutaneously once-daily at any time of day.
- In pediatric patients inject TRESIBA® subcutaneously once-daily at the same time every day.
- Individualize and titrate the dose of TRESIBA® based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- The recommended days between dose increases are 3 to 4 days.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [see *Warnings and Precautions* (5.3)].
- For adult patients, instruct patients who miss a dose of TRESIBA® to inject their daily dose during waking hours upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive TRESIBA® injections.
- For pediatric patients, instruct patients who miss a dose of TRESIBA® to contact their healthcare provider for guidance and to monitor blood glucose levels more frequently until the next scheduled TRESIBA® dose.

2.3 Starting Dose in Insulin Naïve PatientsType 1 Diabetes Mellitus:

The recommended starting dose of TRESIBA® in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus:

The recommended starting dose of TRESIBA® in insulin naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients Already on Insulin TherapyAdults with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA® at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA® at 80% of the total daily long or intermediate-acting insulin unit dose to minimize the risk of hypoglycemia [see *Warnings and Precautions* (5.2)].

3 DOSAGE FORMS AND STRENGTHS

Injection: TRESIBA® is available as a clear and colorless solution:

- 100 units/mL (U-100): 3 mL FlexTouch® disposable prefilled pen
- 200 units/mL (U-200): 3 mL FlexTouch® disposable prefilled pen

4 CONTRAINDICATIONS

TRESIBA® is contraindicated:

- During episodes of hypoglycemia [see *Warnings and Precautions* (5.3)].
- In patients with hypersensitivity to TRESIBA® or one of its excipients [see *Warnings and Precautions* (5.5)].

5 WARNINGS AND PRECAUTIONS**5.1 Never Share a TRESIBA® FlexTouch® Pen Between Patients**

TRESIBA® FlexTouch® disposable prefilled pens should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant anti-diabetic treatment may be needed. When converting from other insulin therapies to TRESIBA® follow dosing recommendations [see *Dosage and Administration* (2.4)].

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including TRESIBA® [see *Adverse Reactions* (6.1)]. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). TRESIBA®, or any insulin, should not be used during episodes of hypoglycemia [see *Contraindications* (4)].

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see *Drug Interactions* (7)], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin [see *Clinical Pharmacology* (12.2)] and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of TRESIBA® may vary among different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions* (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations* (8.6, 8.7)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TRESIBA® and other insulins, instruct patients to always check the insulin label before each injection.

To avoid dosing errors and potential overdose, never use a syringe to remove TRESIBA® from the TRESIBA® pen into a syringe [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.3)].

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TRESIBA®. If hypersensitivity reactions occur, discontinue TRESIBA®; treat per standard of care and monitor until symptoms and signs resolve. TRESIBA® is contraindicated in patients who have had hypersensitivity reactions to insulin degludec or one of the excipients [see *Contraindications* (4)].

5.6 Hypokalemia

All insulin products, including TRESIBA®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin, including TRESIBA®, and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions* (5.3)]
- Medication errors [see *Warnings and Precautions* (5.4)]
- Hypersensitivity and allergic reactions [see *Warnings and Precautions* (5.5)]
- Hypokalemia [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TRESIBA® in subjects with type 1 diabetes or type 2 diabetes was evaluated in nine trials of 6-12 month duration in adults and in one trial of 12-month duration in pediatric patients 1 year of age and older with type 1 diabetes. The cardiovascular safety of TRESIBA® was evaluated in one double-blinded, event-driven trial of 2-year median duration in patients with type 2 diabetes at high risk of cardiovascular events [see *Clinical Studies* (14)].

The data in Table 1 reflect the exposure of 1102 adults with type 1 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 34 weeks in three open-label trials. The mean age was 43

years and 1% were older than 75 years. Fifty-seven percent were male, 81% were White, 2% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 26 kg/m². The mean duration of diabetes was 18 years and the mean HbA_{1c} at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 7% and 0.5% respectively. The mean eGFR at baseline was 87 mL/min/1.73 m² and 7% of the patients had an eGFR less than 60 mL/min/1.73 m².

The data in Table 2 reflect the exposure of 2713 adults with type 2 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 36 weeks in six open-label trials. The mean age was 58 years and 3% were older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African American and 13% were Hispanic. The mean BMI was 30 kg/m². The mean duration of diabetes was 11 years and the mean HbA_{1c} at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 14%, 10%, 6% and 0.6% of participants respectively. At baseline, the mean eGFR was 83 mL/min/1.73 m² and 9% had an eGFR less than 60 mL/min/1.73 m².

Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA® treated subjects during clinical trials in adult patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

174 pediatric patients 1 year of age and older with type 1 diabetes were exposed to TRESIBA® with a mean exposure to TRESIBA® of 48 weeks. The mean age was 10 years: 25% were ages 1-5 years, 40% were ages 6-11 years, and 35% were ages 12-17 years: 55.2% were male, 78.2% were White, 2.9% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 18.7 kg/m². The mean duration of diabetes was 3.9 years and the mean HbA_{1c} at baseline was 8.2%. Common adverse reactions in TRESIBA® treated pediatric patients with type 1 diabetes mellitus were similar to the adverse reactions listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Adult Patients with Type 1 Diabetes Mellitus

Adverse Reaction	TRESIBA® (n=1102)
Nasopharyngitis	23.9 %
Upper respiratory tract infection	11.9 %
Headache	11.8 %
Sinusitis	5.1 %
Gastroenteritis	5.1 %

Table 2: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	TRESIBA® (n=2713)
Nasopharyngitis	12.9 %
Headache	8.8 %
Upper respiratory tract infection	8.4 %
Diarrhea	6.3 %

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TRESIBA® [see *Warnings and Precautions* (5.3)]. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for TRESIBA® with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the open-label adult clinical trials of patients with type 1 and type 2 diabetes, and in the open-label pediatric clinical trial of patients with type 1 diabetes, percentages of adult and pediatric patients with type 1 diabetes randomized to TRESIBA® who experienced at least one episode of hypoglycemia in clinical trials [see *Clinical Studies* (14)] and adults with type 2 diabetes are shown in Tables 3 and 4, respectively.

Severe hypoglycemia in the open-label trials with adult patients was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia in the pediatric trial was defined as an altered mental status where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose). A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: Percent (%) of Type 1 Diabetes Patients Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on TRESIBA® in Open-Label Adult and Pediatric Clinical Trials

	Study A Adults + insulin aspart 52 weeks	Study B Adults + insulin aspart 26 weeks	Study C Adults + insulin aspart 26 weeks		Study J Pediatrics + insulin aspart 52 weeks
	TRESIBA® (N=472)	TRESIBA® (N=301)	TRESIBA® at the same time each day (N=165)	TRESIBA® at alternating times (N=164)	TRESIBA® (N=174)
Severe hypoglycemia*					
Percent of patients	12.3%	10.6%	12.7%	10.4%	17.8%
Novo Nordisk hypoglycemia§					
Percent of patients	95.6%	93.0%	99.4%	93.9%	98.3%

* Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).

[§] Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on TRESIBA® in Open-Label Adult Clinical Trials

Open Label Adult Clinical Trials							
	Study D + 1-2 OADs* insulin naïve 52 weeks	Study E + 1-2 OADs* insulin naïve 26 weeks	Study F + 1-3 OADs* insulin naïve 26 weeks	Study G T2DM ± 0-3 OADs* 26 weeks		Study H T2DM ± 0-2 OADs* + insulin aspart 52 weeks	Study I T2DM ± 1-2 OADs* insulin naïve 26 weeks
	TRESIBA® (N=766)	TRESIBA® (N=228)	TRESIBA® (N=284)	TRESIBA® (N=226)	TRESIBA® (alternating time) (N=230)	TRESIBA® (N=753)	TRESIBA® (N=226)
Severe Hypoglycemia							
Percent of patients	0.3%	0	0	0.9%	0.4%	4.5%	0.4%
Novo Nordisk Hypoglycemia [§]							
Percent of patients	46.5%	28.5%	50%	43.8%	50.9%	80.9%	42.5%

* OAD: oral antidiabetic agent. [§] Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including TRESIBA® and may be life threatening [see *Warnings and Precautions* (5.5)]. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were reported in 0.9% of patients treated with TRESIBA®.

Lipodystrophy

Long-term use of insulin, including TRESIBA®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect insulin absorption [see *Dosage and Administration* (2.1)]. In the clinical program, lipodystrophy, lipohypertrophy, or lipoatrophy was reported in 0.3% of patients treated with TRESIBA®.

Injection Site Reactions

Patients taking TRESIBA® may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass. In the clinical program, injection site reactions occurred in 3.8% of patients treated with TRESIBA®.

Weight Gain

Weight gain can occur with insulin therapy, including TRESIBA®, and has been attributed to the anabolic effects of insulin. In the clinical program after 52 weeks of treatment, patients with type 1 diabetes treated with TRESIBA® gained an average of 1.8 kg and patients with type 2 diabetes treated with TRESIBA® gained an average of 3.0 kg.

Peripheral Edema

Insulin, including TRESIBA®, may cause sodium retention and edema. In the clinical program, peripheral edema occurred in 0.9% of patients with type 1 diabetes mellitus and 3.0% of patients with type 2 diabetes mellitus treated with TRESIBA®.

6.2 Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRESIBA® with the incidence of antibodies in other studies or to other products may be misleading.

In studies of adult type 1 diabetes patients, 95.9% of patients who received TRESIBA® once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7% that

were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received TRESIBA® once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients.

The incidence of anti-insulin degludec antibodies has not been established.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with TRESIBA®.

Table 5: Clinically Significant Drug Interactions with TRESIBA®

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA®	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA®	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with TRESIBA® or insulin degludec in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

Rats and rabbits were exposed to insulin degludec in animal reproduction studies during organogenesis. Pre- and post-implantation losses and visceral/skeletal abnormalities were observed in rats at doses 5 times (rat) and at 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. These effects were similar to those observed in rats administered human insulin (NPH) [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20-25% in women with an HbA_{1c} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryo-fetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. Insulin degludec is present in rat milk [see *Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRESIBA® and any potential adverse effects on the breastfed infant from TRESIBA® or from the underlying maternal condition.

Data

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

8.4 Pediatric Use

The safety and effectiveness of TRESIBA® to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of TRESIBA® have not been established in pediatric patients less than 1 year old.

The use of TRESIBA® in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) [see *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.2)]. The use of TRESIBA® in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus [see *Clinical Studies* (14.3)].

In pediatric patients 1 year of age and older already on insulin therapy, start TRESIBA® at a reduced dose to minimize the risk of hypoglycemia [see *Dosage and Administration* (2.4)].

8.5 Geriatric Use

In controlled clinical studies [see *Clinical Studies* (14)] a total of 77 (7%) of the 1102 TRESIBA®-treated patients with type 1 diabetes were 65 years or older and 9 (1%) were 75 years or older. A total of 670 (25%) of the 2713 TRESIBA®-treated patients with type 2 diabetes were 65 years or older and 80 (3%) were 75 years or older. Differences in safety or effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

In the safety outcomes trial (DEVOTE), a total of 1983 (52%) of the 3818 TRESIBA®-treated patients with type 2 diabetes were 65 years or older and 381 (10%) were 75 years or older. Differences in safety or effectiveness were not observed in these subgroup analyses.

Nevertheless, greater caution should be exercised when TRESIBA® is administered to geriatric patients since greater sensitivity of some older individuals to the effects of TRESIBA® cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.6 Renal Impairment

In clinical studies [see *Clinical Studies* (14)] a total of 75 (7%) of the 1102 TRESIBA®-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m² and 1 (0.1%) had an eGFR less than 30 mL/min/1.73 m². A total of 250 (9%) of the 2713 TRESIBA®-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m² and no subjects had an eGFR less than 30 mL/min/1.73 m².

In the safety outcomes trial (DEVOTE), a total of 1429 (37.4%) of the 3818 TRESIBA®-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m², and 108 (2.8%) subjects had an eGFR less than 30 mL/min/1.73 m². Differences in safety or effectiveness were not observed in the subgroup analyses.

No clinically relevant difference in the pharmacokinetics of TRESIBA® was identified in a study comparing healthy subjects and subjects with renal impairment including subjects with end stage renal disease [see *Clinical Pharmacology* (12.3)]. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA® dosage adjusted on an individual basis in patients with renal impairment.

8.7 Hepatic Impairment

No difference in the pharmacokinetics of TRESIBA® was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) [see *Clinical Pharmacology* (12.3)]. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA® dosage adjusted on an individual basis in patients with hepatic impairment.

10 OVERDOSAGE

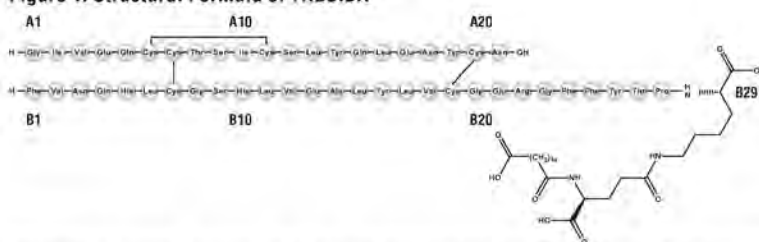
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia [see *Warnings and Precautions* (5.3, 5.6)]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

TRESIBA® (insulin degludec injection) is a long-acting basal human insulin analog for subcutaneous injection. Insulin degludec is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecanoyl-γ-Glu) des(B30) human insulin). Insulin degludec has a molecular formula of C₂₇₄H₄₁₁N₆₅O₈₁S₆ and a molecular weight of 6103.97. It has the following structure:

Figure 1: Structural Formula of TRESIBA®



TRESIBA® is a sterile, aqueous, clear, and colorless solution that contains insulin degludec 100 units/mL (U-100) or 200 units/mL (U-200).

Inactive ingredients for the 100 units/mL are: glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 32.7 mcg/mL and water for injection.

Inactive ingredients for the 200 units/mL are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 71.9 mcg/mL and water for injection.

TRESIBA® has a pH of approximately 7.6. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

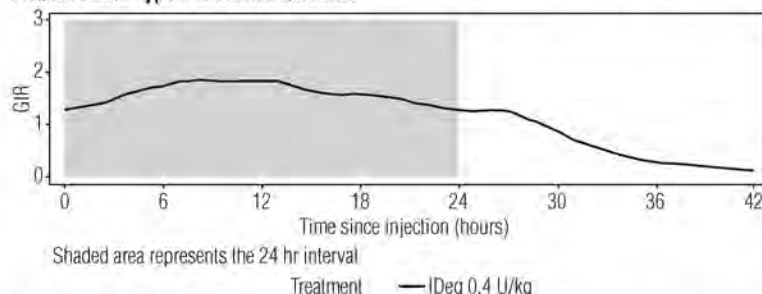
12.1 Mechanism of Action

The primary activity of insulin, including TRESIBA®, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. TRESIBA® forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of TRESIBA® is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

12.2 Pharmacodynamics

The glucose-lowering effect of TRESIBA® after 8 days of once-daily dosing was measured in a euglycemic glucose clamp study enrolling 21 patients with type 1 diabetes. Figure 2 shows the pharmacodynamic effect of TRESIBA® over time following 8 once-daily subcutaneous injections of 0.4 U/kg of TRESIBA® in patients with type 1 diabetes.

Figure 2: Mean GIR Profile for 0.4 units/kg Dose of TRESIBA® (Steady State) in Patients with Type 1 Diabetes Mellitus



The mean maximum glucose lowering effect (GIR_{max}) of a 0.4 units/kg dose of TRESIBA® was 2.0 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect of TRESIBA® lasted at least 42 hours after the last of 8 once-daily injections.

In patients with type 1 diabetes mellitus, the steady-state, within subjects, day-to-day variability in total glucose lowering effect was 20% with TRESIBA® (within-subject coefficient of variation for $AUC_{GIR, \tau, SS}$).

The total glucose-lowering effect of TRESIBA® over 24 hours measured in a euglycemic clamp study after 8 days of once-daily administration in patients with type 1 diabetes increases approximately in proportion to the dose for doses between 0.4 units/kg to 0.8 units/kg.

The total glucose-lowering effect of 0.4 units/kg of TRESIBA® U-100 and 0.4 units/kg of TRESIBA® U-200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study after 8 days of once-daily injection was comparable.

12.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 units/kg of TRESIBA®, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (t_{max}). After the first dose of TRESIBA®, median onset of appearance was around one hour.

Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 units/kg to 0.8 units/kg TRESIBA®. Total and maximum insulin degludec exposure at steady state are comparable between TRESIBA® U-100 and TRESIBA® U-200 when each is administered at the same units/kg dose.

Insulin degludec concentration reached steady state levels after 3-4 days of TRESIBA® administration [see Dosage and Administration (2.2)].

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. The results of the *in vitro* protein binding studies demonstrate that there is no clinically relevant interaction between insulin degludec and other protein bound drugs.

Elimination

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. On average, the half-life at steady state is approximately 25 hours independent of dose. Degradation of TRESIBA® is similar to that of insulin human; all metabolites formed are inactive. The mean apparent clearance of insulin degludec is 0.03 L/kg (2.1 L/h in 70 kg individual) after single subcutaneous dose of 0.4 units/kg.

Specific Populations

Pediatrics

Population pharmacokinetic analysis was conducted for TRESIBA® using data from 199 pediatric subjects (1 to <18 years of age) with type 1 diabetes. Body weight was a significant covariate affecting the clearance of TRESIBA®. After adjusting for body weight, the total exposure of TRESIBA® at steady state was independent of age.

Geriatrics

Pharmacokinetic and pharmacodynamic response of TRESIBA® was compared in 13 younger adult (18–35 years) and 14 geriatric (≥ 65 years) subjects with type 1 diabetes following two 6-day periods of once-daily subcutaneous dosing with 0.4 units/kg dose of TRESIBA® or insulin glargine. On average, the pharmacokinetic and pharmacodynamic properties of TRESIBA® at steady-state were similar in younger adult and geriatric subjects, albeit with greater between subject variability among the geriatric subjects.

Gender

The effect of gender on the pharmacokinetics of TRESIBA® was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA®.

Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

Obesity

The effect of BMI on the pharmacokinetics of TRESIBA® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA®. For subjects with type 1 diabetes, no relationship between exposure of TRESIBA® and BMI was observed. For subjects with type 1 and type 2 diabetes a trend for decrease in glucose-lowering effect of TRESIBA® with increasing BMI was observed.

Race and Ethnicity

TRESIBA® has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin ($n=18$), White subjects of Hispanic or Latino origin ($n=22$) and White subjects not of Hispanic or Latino origin ($n=23$) with type 2 diabetes mellitus conducted using unit/kg doses of TRESIBA®. There were no statistically significant differences in the pharmacokinetic and pharmacodynamic properties of TRESIBA® between the racial and ethnic groups investigated.

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRESIBA® has not been studied [see Use in Specific Populations (8.1)].

Renal Impairment

TRESIBA® pharmacokinetics was studied in 32 subjects ($n=4-8$ /group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA®. Renal function was defined using creatinine clearance (Cl_{cr}) as follows: ≥ 90 mL/min (normal), 60–89 mL/min (mild), 30–59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{(0-24h, SS)}$) and peak exposure of TRESIBA® were on average about 10–25% and 13–27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of TRESIBA® ($Cl/F_{(0-24h, SS)}$) in subjects with ESRD [see Use in Specific Populations (8.6)].

Hepatic Impairment

TRESIBA® has been studied in a pharmacokinetic study in 24 subjects ($n=6$ /group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA®. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No differences in the pharmacokinetics of TRESIBA® were identified between healthy subjects and subjects with hepatic impairment [see Use in Specific Populations (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study including human insulin (NPH insulin) as comparator (6.7 units/kg/day), Sprague-Dawley rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 units/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 units/kg/day. Human insulin was dosed at 6.7 units/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. Further, no treatment related changes in the occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when compared to vehicle or human insulin.

Genotoxicity testing of insulin degludec was not performed.

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 units/kg/day (approximately 5 times the human subcutaneous dose of 0.75 units/kg/day, based on units/body surface area) prior to mating and in female rats during gestation had no effect on mating performance and fertility.

14 CLINICAL STUDIES

The efficacy of TRESIBA® administered once-daily either at the same time each day or at any time each day in patients with type 1 diabetes and used in combination with a mealtime insulin was evaluated in three randomized, open-label, treat-to-target, active-controlled trials in adults and one randomized, open-label, treat-to-target, active-controlled trial in pediatric patients 1 year of age and older. The efficacy of TRESIBA® administered once-daily either at the same time each day or at any time each day in adult patients with type 2 diabetes and used in combination with a mealtime insulin or in combination with common oral anti-diabetic agents was evaluated in six randomized, open-label, treat-to-target active-controlled trials.

Adult patients treated with TRESIBA® achieved levels of glycemic control similar to those achieved with LANTUS® (insulin glargine 100 units/mL) and LEVEMIR® (insulin detemir) and achieved statistically significant improvements compared to sitagliptin.

14.1 Type 1 Diabetes – Adult

TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

Study A

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial in 629 patients with type 1 diabetes mellitus (Study A). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 58.5% were male. 93% were White, 1.9% Black or African American, 5.1% were Hispanic, 8.6% of patients had $eGFR < 60$ mL/min/1.73m². The mean BMI was approximately 26.3 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was -0.01% with a 95% confidence interval of [-0.14%; 0.11%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study A.

Study B

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 455 patients with type 1 diabetes mellitus (Study B). Patients were randomized to TRESIBA® or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed twice-daily. 67.1% used insulin detemir once daily at end of trial. 32.9% used insulin detemir twice daily at end of trial. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 13.9 years. 51.9% were male, 44.6% were White, 0.4% Black or African American, 4.4% were Hispanic, 4.4% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 23.9 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin detemir was -0.09% with a 95% confidence interval of [-0.23%; 0.05%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study B.

Table 6: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 (Study A) and Week 26 in a Trial Comparing TRESIBA® to Insulin Detemir (Study B) in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	Study A		Study B	
	TRESIBA® + Insulin aspart	Insulin glargine U-100 + Insulin aspart	TRESIBA® + Insulin aspart	Insulin detemir + Insulin aspart
N	472	157	302	153
HbA_{1c} (%)				
Baseline	7.7	7.7	8.0	8.0
End of trial	7.3	7.3	7.3	7.3
Adjusted mean change from baseline*	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference [95%CI] TRESIBA® - basal insulin U-100	-0.01 [-0.14; 0.11]		-0.09 [-0.23; 0.05]	
Proportion Achieving HbA_{1c} < 7% at Trial End	39.8%	42.7%	41.1%	37.3%
FPG (mg/dL)				
Baseline	165	174	178	171
End of trial	141	149	131	161
Adjusted mean change from baseline	-27.6	-21.6	-43.3	-13.5
Daily basal insulin dose				
Baseline mean	28 U	26 U	22 U	22 U
Mean dose at end of study	29 U ¹	31 U ¹	25 U ²	29 U ²
Daily bolus insulin dose				
Baseline mean	29 U	29 U	28 U	31 U
Mean dose at end of study	32 U ¹	35 U ¹	36 U ²	41 U ²

¹At Week 52

²At Week 26

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

In Study A, there were 14.8% of subjects in the TRESIBA® and 11.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

In Study B, there were 6.3% of subjects in the TRESIBA® and 9.8% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

Study C: TRESIBA® Administered at the Same Time Each Day or at Any Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to TRESIBA® injected once-daily at the same time each day (with the main evening meal), to TRESIBA® injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Insulin aspart was administered before each meal in all treatment arms.

The mean age of the trial population was 43.7 years and mean duration of diabetes was 18.5 years. 57.6% were male, 97.6% were White, 1.8% Black or African American, 3.4% were Hispanic, 7.4% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 26.7 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® administered at alternating times and insulin glargine U-100 was 0.17% with a 95% confidence interval of [0.04%; 0.30%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

Table 7: Results at Week 26 in a Trial Comparing TRESIBA® Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin Glargine U-100 in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA® at the same time each day + Insulin aspart	TRESIBA® at alternating times + Insulin aspart	Insulin glargine U-100 + Insulin aspart
N	165	164	164
HbA_{1c} (%)			
Baseline	7.7	7.7	7.7
End of trial	7.3	7.3	7.1
Adjusted mean change from baseline*	-0.41	-0.40	-0.57
Estimated treatment difference [95%CI] TRESIBA® alternating - Insulin glargine U-100	0.17 [0.04; 0.30]		
Proportion Achieving HbA_{1c} < 7% at Trial End	37.0%	37.2%	40.9%
FPG (mg/dL)			
Baseline	179	173	175
End of trial	133	149	151
Adjusted mean change from baseline	-41.8	-24.7	-23.9
Daily basal insulin dose			
Baseline mean	28 U	29 U	29 U
Mean dose at end of study	32 U	36 U	35 U
Daily bolus insulin dose			
Baseline mean	29 U	33 U	32 U
Mean dose at end of study	27 U	30 U	35 U

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

In Study C, there were 15.8% and 15.9% of subjects in the TRESIBA® (same time and alternating times respectively) and 7.9% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

14.2 Type 1 Diabetes – Pediatric Patients 1 Year of Age and Older

Study J: TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Pediatric Patients 1 Year of Age and Older

The efficacy of TRESIBA® was evaluated in a 26-week, randomized, open label, multicenter trial in 350 patients with type 1 diabetes mellitus (Study J). Patients were randomized to TRESIBA® once-daily or insulin detemir once or twice-daily. Subjects on a twice-daily insulin detemir regimen were dosed at breakfast and in the evening either with the main evening meal or at bedtime. Insulin aspart was administered before each main meal in both treatment arms. At end of trial, 36% used insulin detemir once daily and 64% used insulin detemir twice daily.

The mean age of the trial population was 10 years; 24% were ages 1-5 years; 39% were ages 6-11 years and 36% were ages 12-17 years. The mean duration of diabetes was 4 years. 55.4% were male, 74.6% were White, 2.9% Black or African American, 2.9% were Hispanic. The mean z-score for body weight was 0.31.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin detemir was 0.15% with a 95% confidence interval of [-0.03%; 0.33%] and met the pre-specified non-inferiority margin (0.4%). See Table 8.

Table 8: Results at Week 26 in a Trial Comparing TRESIBA® to Insulin Detemir in Pediatric Patients 1 Year of Age and Older with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA® + Insulin aspart	Insulin detemir + Insulin aspart
N	174	176
HbA_{1c} (%)		
Baseline	8.2	8.0
End of 26 weeks	8.0	7.7
Adjusted mean change from baseline after 26 weeks*	-0.19	-0.34
Estimated treatment difference [95%CI] TRESIBA® v. Insulin detemir	0.15 [-0.03; 0.33]	
FPG (mg/dL)		
Baseline	162	151
End of 26 weeks	150	160
Adjusted mean change from baseline after 26 weeks	52.0	59.6
Daily basal insulin dose		
Baseline mean	15 U (0.37 U/kg)	16 U (0.41 U/kg)
Mean dose after 26 weeks	16 U (0.37 U/kg)	22 U (0.51 U/kg)
Daily bolus insulin dose		
Baseline mean	20 U (0.50 U/kg)	20 U (0.52 U/kg)
Mean dose after 26 weeks	23 U (0.56 U/kg)	22 U (0.57 U/kg)

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with missing data imputed by multiple imputation carrying forward the baseline value and adding the error term, with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate.

In Study J, there were 2.9% of subjects in TRESIBA® and 6.3% Insulin detemir arms for whom data was missing at the 26-week HbA_{1c} measurement.

14.3 Type 2 Diabetes – Adult

Study D: TRESIBA® Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Metformin alone (82.5%) or in combination with a DPP-4 inhibitor (17.5%) was used as background therapy in both treatment arms.

The mean age of the trial population was 59.1 years and mean duration of diabetes was 9.2 years. 61.9% were male. 88.4% were White, 7.1% Black or African American, 17.2% were Hispanic. 9.6% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 31.1 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.09% with a 95% confidence interval of [-0.04%; 0.22%] and met the pre-specified non-inferiority margin (0.4%); See Table 9.

Table 9: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® + OAD(s)*	Insulin glargine U-100 + OAD(s)*
N	773	257
HbA_{1c} (%)		
Baseline	8.2	8.2
End of trial	7.1	7.0
Adjusted mean change from baseline**	-1.06	-1.15
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.09 [-0.04; 0.22]	
Proportion Achieving HbA_{1c} < 7% at Trial End	51.7%	54.1%
FPG (mg/dL)		
Baseline	174	174
End of trial	106	115
Adjusted mean change from baseline	-68.0	-60.2
Daily insulin dose		
Baseline mean (starting dose)	10 U	10 U
Mean dose after 52 weeks	56 U	58 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study D, there were 20.6% of subjects in the TRESIBA® and 22.2% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study E: TRESIBA® U-200 Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA® U-200 was evaluated in a 26-week randomized, open-label, multicenter trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® U-200 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Both treatment arms were receiving metformin alone (84%) or in combination with a DPP-4 inhibitor (16%) as background therapy.

The mean age of the trial population was 57.5 years and mean duration of diabetes was 8.2 years. 53.2% were male. 78.3% were White, 13.8% Black or African American, 7.9% were Hispanic. 7.5% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 32.4 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® U-200 and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.11%; 0.19%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

Table 10: Results at Week 26 in a Trial Comparing TRESIBA® U-200 to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® U-200 + Met ± DPP-4	Insulin glargine U-100 + Met ± DPP-4
N	228	229
HbA_{1c} (%)		
Baseline	8.3	8.2
End of trial	7.0	6.9
Adjusted mean change from baseline**	-1.18	-1.22
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.04 [-0.11; 0.19]	
Proportion Achieving HbA_{1c} < 7% at Trial End	52.2%	55.9%
FPG (mg/dL)		
Baseline	172	174
End of trial	106	113
Adjusted mean change from baseline	-71.1	-63.5
Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	59 U	62 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study E, there were 12.3% of subjects in the TRESIBA® and 12.7% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study F: TRESIBA® Administered at the Same Time Each Day in Insulin Naïve Adult Patients as an Add-on to One or More of the Following Oral Agents: Metformin, Sulfonylurea, Glinides or Alpha-Glucosidase Inhibitors

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in Asia in 435 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® once-daily in the evening or insulin glargine U-100 once-daily according to the approved labeling. Pre-trial oral antidiabetic agents were continued as background therapy except for DPP-4 inhibitors or thiazolidinediones in both treatment arms.

The mean age of the trial population was 58.6 years and mean duration of diabetes was 11.6 years. 53.6% were male. All patients were Asian. 10.9% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 25.0 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.11% with a 95% confidence interval of [-0.03%; 0.24%] and met the pre-specified non-inferiority margin (0.4%). See Table 11.

Table 11: Results at Week 26 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® + OAD(s)*	Insulin glargine U-100 + OAD(s)*
N	289	146
HbA_{1c} (%)		
Baseline	8.4	8.5
End of trial	7.2	7.1
Adjusted mean change from baseline**	-1.42	-1.52
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.11 [-0.03; 0.24]	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	48.6%
FPG (mg/dL)		
Baseline	152	156
End of trial	100	102
Adjusted mean change from baseline	-54.6	-53.0
Daily insulin dose		
Baseline mean (starting dose)	9 U	9 U
Mean dose after 26 weeks	19 U	24 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study F, there were 10% of subjects in the TRESIBA® and 6.8% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study G: TRESIBA® Administered at the Same Time Each Day or Any Time Each Day as an Add-on to One and up to Three of the Following Oral Agents: Metformin, Sulfonylurea or Glinides or Pioglitazone in Adult Patients

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 687 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone, oral antidiabetic agents (OADs) alone or both basal insulin and OAD. Patients were randomized to TRESIBA® injected once-daily at the same time each day (with the main evening meal), to TRESIBA® injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Up to three of the following oral antidiabetic agents (metformin, sulfonylureas, glinides or thiazolidinediones) were administered as background therapy in both treatment arms.

The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6 years. 53.9% were male. 66.7% were White, 2.5% Black or African American, 10.6% were Hispanic. 5.8% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 29.6 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® at alternating times and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.12%; 0.20%]. This comparison met the pre-specified non-inferiority margin (0.4%). See Table 12.

Table 12: Results at Week 26 in a Trial Comparing TRESIBA® at Same and Alternating Times to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® at the same time each day ± OAD(s)*	TRESIBA® at alternating times ± OAD(s)*	Insulin glargine U-100 ± OAD(s)*
N	228	229	230
HbA_{1c} (%)			
Baseline	8.4	8.5	8.4
End of trial	7.3	7.2	7.1
Adjusted mean change from baseline**	-1.03	-1.17	-1.21
Estimated treatment difference [95%CI] TRESIBA® alternating - Insulin glargine U-100	0.04 [-0.12; 0.20]		
Estimated treatment difference TRESIBA® alternating - TRESIBA® same	-0.13		
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	38.9%	43.9%
FPG (mg/dL)			
Baseline	158	162	163
End of trial	105	105	112
Adjusted mean change from baseline	-54.2	-55.0	-47.5
Daily insulin dose			
Baseline mean	21 U	19 U	19 U
Mean dose after 26 weeks	45 U	46 U	44 U

*OAD: oral antidiabetic agent

The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study G, there were 11.4% subjects for TRESIBA® (both same time and alternating times) and 11.7% insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.Study H: TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients**

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial in 992 patients with type 2 diabetes mellitus inadequately controlled on premix insulin, bolus insulin alone, basal insulin alone, oral antidiabetic agents (OADs) alone or any combination thereof. Patients were randomized to TRESIBA® once-daily with the main evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms. Up to two of the following oral antidiabetic agents (metformin or pioglitazone) were used as background therapy in both treatment arms.

The mean age of the trial population was 58.9 years and mean duration of diabetes was 13.5 years. 54.2% were male. 82.9% were White, 9.5% Black or African American. 12.0% were Hispanic. 12.4% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 32.2 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.08% with a 95% confidence interval of [-0.05%; 0.21%] and met the pre-specified non-inferiority margin (0.4%). See Table 13.

Table 13: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes and OADs*

	TRESIBA® + Insulin aspart ± OAD(s)*	Insulin glargine U-100 + Insulin aspart ± OAD(s)*
N	744	248
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline**	-1.10	-1.18
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.08 [-0.05; 0.21]	
Proportion Achieving HbA_{1c} < 7% at Trial End	49.5%	50.0%
FPG (mg/dL)		
Baseline	166	166
End of trial	122	127
Adjusted mean change from baseline	-40.6	-35.3
Daily basal insulin dose		
Baseline mean	42 U	41 U
Mean dose after 52 weeks	74 U	67 U
Daily bolus insulin dose		
Baseline mean	33 U	33 U
Mean dose after 52 weeks	70 U	73 U

*OAD: oral antidiabetic agent

The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study H, there were 16.1% of subjects in the TRESIBA® and 14.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.Study I: TRESIBA® Administered at Any Time Each Day as an Add-on to One or Two of the Following Oral Agents: Metformin, Sulfonylurea, or Pioglitazone in Adult Patients**

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agent (OADs) at baseline. Patients were randomized to TRESIBA® once-daily at any time of day or sitagliptin once-daily according to the approved labeling. One or two of the following oral antidiabetic agents (metformin, sulfonylurea or pioglitazone) were also administered in both treatment arms.

The mean age of the trial population was 55.7 years and mean duration of diabetes was 7.7 years. 58.6% were male. 61.3% were White, 7.6% Black or African American. 21.0% were Hispanic. 6% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 30.4 kg/m².

At the end of 26 weeks, TRESIBA® provided greater reduction in mean HbA_{1c} compared to sitagliptin (p < 0.001). See Table 14.

Table 14: Results at Week 26 in a Trial Comparing TRESIBA® to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus on OADs*

	TRESIBA® + OAD(s)*	Sitagliptin + OAD(s)*
N	225	222
HbA_{1c} (%)		
Baseline	8.8	9.0
End of trial	7.2	7.7
Adjusted mean change from baseline**	-1.52	-1.09
Estimated treatment difference [95%CI] TRESIBA® - Sitagliptin	-0.43 [-0.61; -0.24]†	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.9%	27.9%
FPG (mg/dL)		
Baseline	170	179
End of trial	112	154
Adjusted mean change from baseline	-61.4	-22.3
Daily insulin dose		
Baseline mean	10 U	N/A
Mean dose after 26 weeks	43 U	N/A

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.†In Study I, there were 20.9% of subjects in the TRESIBA® and 22.5% Sitagliptin arms for whom data was missing at the time of the HbA_{1c} measurement.

†p < 0.001; 1-sided p-value evaluated at 2.5% level for superiority

14.4 Safety Outcomes Trial**DEVOTE (NCT01959529) Cardiovascular Outcomes Trial of TRESIBA® Administered Once-Daily Between Dinner and Bedtime in Combination with Standard of Care in Subjects with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease**

DEVOTE was a multi-center, multi-national, randomized, double-blinded, active-controlled, treat-to-target, event-driven trial. 7,637 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to either TRESIBA® or insulin glargine U-100. Each was administered once-daily between dinner and bedtime in addition to standard of care for diabetes and cardiovascular disease for a median duration of 2 years.

Patients eligible to enter the trial were; 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

At baseline, demographic and disease characteristics were balanced between treatment groups. The mean age of the trial population was 65 years and the mean duration of diabetes was 16.4 years. The population was 62.6% male, 75.6% White, 10.9% Black or African American, 10.2% Asian. 14.9% had Hispanic ethnicity. The mean HbA_{1c} was 8.4% and the mean BMI was 33.6 kg/m². The baseline mean estimated glomerular filtration rate (eGFR) was 68 mL/min/1.73m². 41% of patients had eGFR 60-90 mL/min/1.73m²; 35% of patients had eGFR 30 to 60 mL/min/1.73m² and 3% of patients had eGFR < 30 mL/min/1.73m². Previous history of severe hypoglycemia was not captured in the trial.

At baseline, patients treated their diabetes with oral antidiabetic drugs (72%) and with an insulin regimen (84%). Types of insulins included long acting insulin (60%), intermediate acting insulin (14%) short acting insulin (37%) and premixed insulin (10%). 16% of patients were insulin naïve. The most common background oral antidiabetic drugs used at baseline were metformin (60%), sulfonylureas (29%) and DPP-4 inhibitors (12%).

During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets for lipids and blood pressure.

Cardiovascular Outcomes - Patients with T2DM and Atherosclerotic CVD

The incidence of major cardiovascular events with TRESIBA® was evaluated in DEVOTE. Subjects treated with TRESIBA® had a similar incidence of major adverse cardiovascular events (MACE) when compared to those treated with insulin glargine U-100.

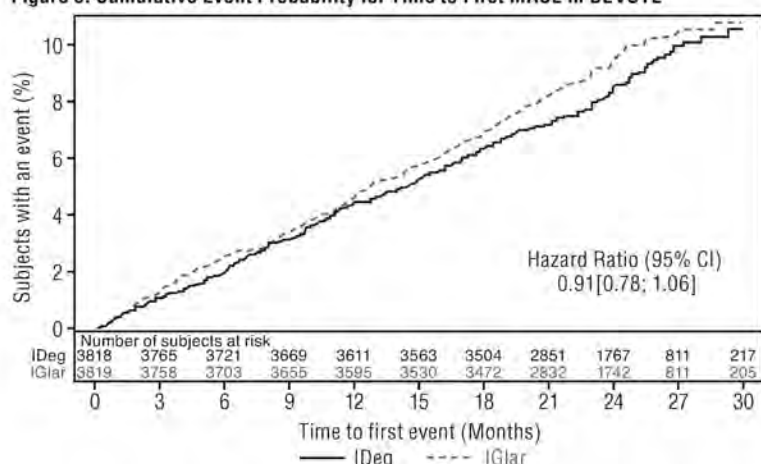
The primary endpoint in DEVOTE was time from randomization to the first occurrence of a 3-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE comparing TRESIBA® to insulin glargine U-100. The primary outcome at end of trial was available for 98.2% of participants in each treatment group.

The time to first occurrence of MACE with TRESIBA® as compared to insulin glargine U-100 was non-inferior (HR: 0.91; 95% CI [0.78; 1.06]; see Figure 3). The results of the primary composite MACE endpoint and a summary of its individual components are shown in Table 15.

Table 15: Analysis of the Composite 3-point MACE and Individual Cardiovascular Endpoints in DEVOTE

N	TRESIBA®		Insulin glargine U-100		Hazard Ratio (95% CI)
	3818	3819	3818	3819	
	Number of Patients (%)	Rate per 100 PYO*	Number of Patients (%)	Rate per 100 PYO*	
Composite of first event of CV death, non-fatal MI, or non-fatal stroke (3-Point MACE)	325 (8.5)	4.41	356 (9.3)	4.86	0.91 [0.78; 1.06]
CV death	136 (3.6)	1.85	142 (3.7)	1.94	
Non-fatal MI	144 (3.8)	1.95	169 (4.4)	2.31	
Non-fatal stroke	71 (1.9)	0.96	79 (2.1)	1.08	

*PYO = patient-years of observation until first MACE, death, or trial discontinuation

Figure 3: Cumulative Event Probability for Time to First MACE in DEVOTE**Hypoglycemia Outcomes - Patients with T2DM and Atherosclerotic CVD**

The pre-specified secondary endpoints of event and incidence rates of severe hypoglycemia were sequentially tested.

Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The incidence of severe hypoglycemia was lower in the TRESIBA® group as compared to the insulin glargine U-100 group (Table 16). Glycemic control between the two groups was similar at baseline and throughout the trial.

Table 16: Severe Hypoglycemic Episodes in Patients Treated with TRESIBA® or Insulin Glargine U-100 in DEVOTE

	TRESIBA®	Insulin glargine U-100
N	3818	3819
Severe Hypoglycemia		
Percent of patients with events	4.9%	6.6%
Estimated odds ratio [95%CI] TRESIBA®/Insulin glargine U-100	0.73 [0.60; 0.89]*	
Events per 100 Patient Years of Observation	3.70	6.25
Estimated rate ratio [95%CI] TRESIBA®/Insulin glargine U-100	0.60 [0.48; 0.76]*	

* Test for superiority evaluated at 5% level for significance, (2-sided p<0.001)

16 HOW SUPPLIED/STORAGE AND HANDLING**16.1 How Supplied**

TRESIBA® is available as a clear and colorless solution in the following package sizes (see Table 17).

Table 17: Presentations of TRESIBA®

TRESIBA®	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Package Size
U-100 FlexTouch®	3 mL	100 units/mL	300 Units	0169-2660-15	80 Units	1 Unit	5 pens/package
U-200 FlexTouch®	3 mL	200 units/mL	600 Units	0169-2550-13	160 Units	2 Unit	3 pens/package

16.2 Recommended Storage

Unused TRESIBA® should be stored in a refrigerator (36°F to 46°F [2°C to 8°C]). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use TRESIBA® if it has been frozen.

The storage conditions are summarized in Table 18:

Table 18: Storage Conditions for TRESIBA® FlexTouch®

	Not in-use (unopened)		In-use (opened)	
	Refrigerated (36°F to 46°F [2°C to 8°C])	Room Temperature (below 86°F [30°C])	Room Temperature (below 86°F [30°C])	Refrigerated (36°F to 46°F [2°C to 8°C])
3 mL TRESIBA® U-100 FlexTouch®	Until expiration date	56 days (8 weeks)	56 days (8 weeks)	56 days (8 weeks)
3 mL TRESIBA® U-200 FlexTouch®	Until expiration date	56 days (8 weeks)	56 days (8 weeks)	56 days (8 weeks)

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share a TRESIBA® FlexTouch® Pen Between Patients

Advise patients that they should never share a TRESIBA® FlexTouch®, pen device with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens [see Warnings and Precautions (5.1)].

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia.

Advise patients that changes in insulin regimen should be made under close medical supervision [see Warnings and Precautions (5.2)].

Medication Errors

Inform patients to always check the insulin label before each injection [see Warnings and Precautions (5.4)]. Inform patients that the dose counter of TRESIBA® FlexTouch® pen shows the number of units of TRESIBA® to be injected. NO dose re-calculation is required [see Dosage and Administration (2.2)]. Instruct patients to never use a syringe to remove TRESIBA® from the FlexTouch® disposable insulin prefilled pen.

Women of Reproductive Potential

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Rx Only

Date of Issue: 03/2018

Version: 5

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PATENT Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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DK-2880 Bagsvaerd, Denmark

For information about TRESIBA® contact:

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www.novonordisk-us.com

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USA18TSM01155 April 2018

Patient Information
TRESIBA® (tre-SI-bah)
 (insulin degludec injection)

Do not share your TRESIBA® FlexTouch® insulin delivery device with other people, even if the needle has changed. You may give other people a serious infection, or get a serious infection from them.

What is TRESIBA®?

- TRESIBA® is a man-made insulin that is used to control high blood sugar in adults and children who are 1 year of age and older with diabetes mellitus.
- TRESIBA® is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- TRESIBA® is not for children who need less than 5 units of TRESIBA® each day.
- It is not known if TRESIBA® is safe and effective in children under 1 year of age.
- TRESIBA® is available in 2 concentrations: The 100 units/mL pen can be injected from 1 to 80 units in a single injection, in increments of 1 unit. The 200 units/mL pen can be injected from 2 to 160 units in a single injection, in increments of 2 units.

Who should not take TRESIBA®?

Do not take TRESIBA® if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to TRESIBA® or any of the ingredients in TRESIBA®.

Before taking TRESIBA®, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking TRESIBA®, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take TRESIBA®?

- **Read the Instructions for Use** that come with your TRESIBA®.
- Take TRESIBA® exactly as your healthcare provider tells you to.
- **Do not do any conversion of your dose. The dose counter always shows the selected dose in units.** Both the 100 units/mL and 200 units/mL TRESIBA® FlexTouch® pens are made to deliver your insulin dose in units.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- **Adults:** If you miss or are delayed in taking your dose of TRESIBA®:
 - Take your dose as soon as you remember then continue with your regular dosing schedule.
 - Make sure there are at least **8** hours between your doses.
- If children miss a dose of TRESIBA®:
 - Call the healthcare provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of TRESIBA®.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share your needles with other people.** You may give other people a serious infection or get a serious infection from them.
- **Never** inject TRESIBA® into a vein or muscle.
- **Never** use a syringe to remove TRESIBA® from the FlexTouch® pen.

What should I avoid while taking TRESIBA®?

While taking TRESIBA® do not:

- Drive or operate heavy machinery, until you know how TRESIBA® affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of TRESIBA®?

TRESIBA® may cause serious side effects that can lead to death, including:

- **Low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
 - dizziness or light-headedness
 - blurred vision
 - anxiety, irritability, or mood changes
 - sweating
 - slurred speech
 - hunger
 - confusion
 - shakiness
 - headache
 - fast heartbeat
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with TRESIBA® may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with TRESIBA®. Your healthcare provider should monitor you closely while you are taking TZDs with TRESIBA®. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, tiredness, swelling of your ankles or feet and sudden weight gain. Treatment with TZDs and TRESIBA® may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Common side effects of TRESIBA® may include:

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of TRESIBA®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRESIBA®.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRESIBA® that is written for health professionals. Do not use TRESIBA® for a condition for which it was not prescribed. Do not give TRESIBA® to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in TRESIBA®?

Active Ingredient: insulin degludec

Inactive Ingredients: zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: 12/2016

Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 200 units/mL
(insulin degludec injection)

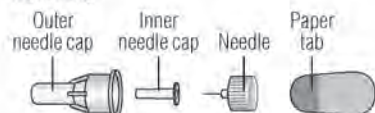
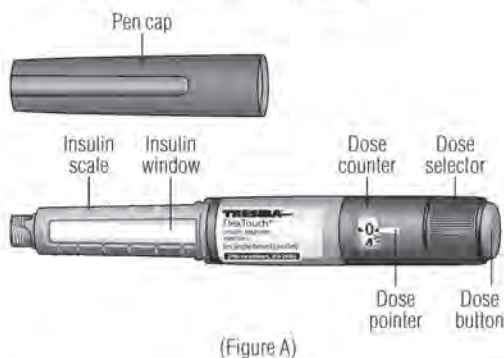
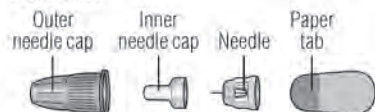
- Do not share your TRESIBA® FlexTouch® Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.
- TRESIBA® FlexTouch® Pen 200 units/mL ("Pen") is a prefilled disposable pen containing 600 units of TRESIBA® (insulin degludec injection) 200 units/mL insulin. You can inject from 2 to 160 units in a single injection. The units can be increased by 2 units at a time.
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your TRESIBA® injection:

- TRESIBA® FlexTouch® Pen
- a new NovoFine® or NovoTwist® needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See "After your injection" at the end of these instructions.

Preparing your TRESIBA® FlexTouch® Pen:

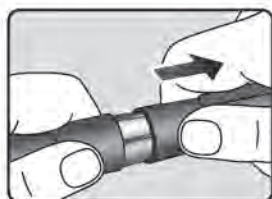
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the TRESIBA® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- TRESIBA® should look clear and colorless. Do not use TRESIBA® if it is cloudy or colored.
- Do not use TRESIBA® past the expiration date printed on the label or 56 days after you start using the Pen.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.

NovoFine®**NovoTwist®**

(Figure A)

Step 1:

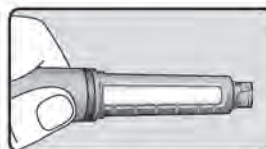
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

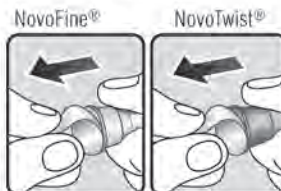
- Check the liquid in the Pen (See Figure C). TRESIBA® should look clear and colorless. Do not use it if it looks cloudy or colored.



(Figure C)

Step 3:

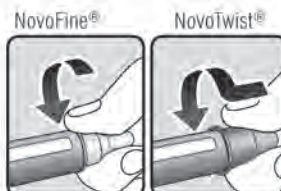
- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

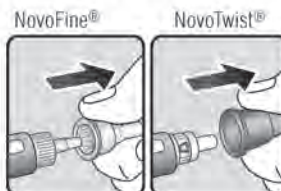
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

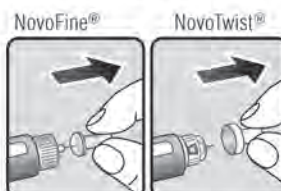
- Pull off the outer needle cap. Do not throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA® FlexTouch® Pen:**Step 7:**

- Turn the dose selector to select 2 units (See Figure H).



(Figure H)

Step 8:

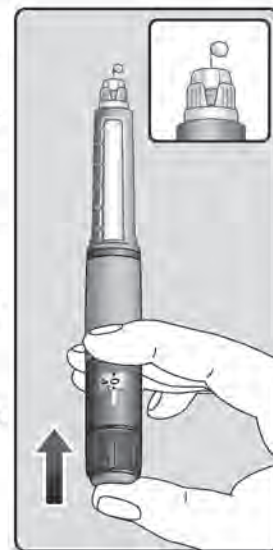
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

Step 9:

- Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
 - If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
 - If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.



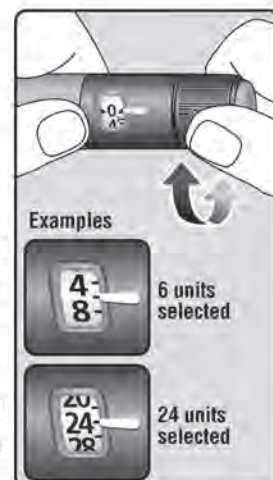
(Figure J)

Selecting your dose:**Step 10:**

TRESIBA® FlexTouch® Pen 200 units/mL is made to deliver the number of units of insulin that your healthcare provider prescribed. Do not perform any dose conversion.

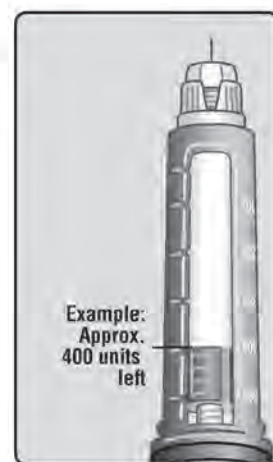
Check to make sure the dose selector is set at 0.

- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
 - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
 - Each line on the dial is an even number.



(Figure K)

- The TRESIBA® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

- To see how much insulin is left in your TRESIBA® FlexTouch® Pen:

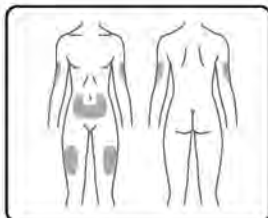
- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 160, there are at least 160 units left in your Pen.
- If the dose counter shows less than 160, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your TRESIBA® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA® can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

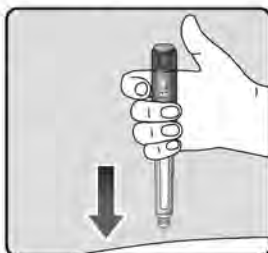
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

Step 12:

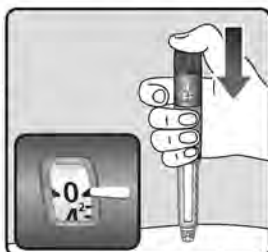
- Insert the needle into your skin** (See Figure N).
 - Make sure you can see the dose counter.** Do not cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

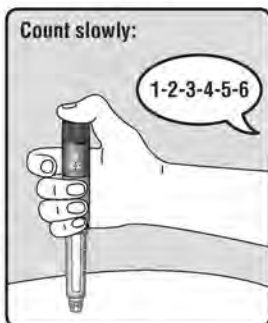
- Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
 - The "0" must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

- Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6** (See Figure P).

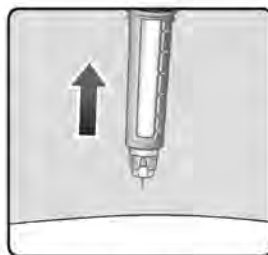
- When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
- If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
- If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



(Figure P)

Step 14:

- Pull the needle out of your skin** (See Figure Q).
 - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

Step 15:

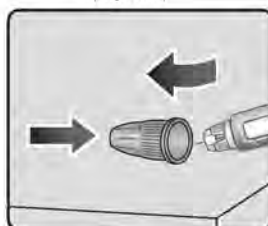
- Carefully remove the needle from the Pen and throw it away** (See Figure R).
 - Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

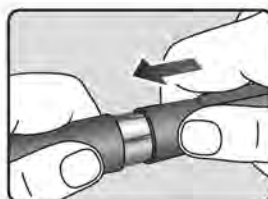
- Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.



(Figure S)

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used TRESIBA® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my TRESIBA® FlexTouch® Pen?**Before use:**

- Store unused TRESIBA® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not** freeze TRESIBA®. **Do not** use TRESIBA® if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA®.

- Keep TRESIBA® FlexTouch® Pens and needles out of the reach of children.**
- Always** use a new needle for each injection.
- Do not** share TRESIBA® FlexTouch® Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 12/2016

For more information go to
www.TRESIBA.com

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USA18TSM01155 April 2018



Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 100 units/mL
(insulin degludec injection)

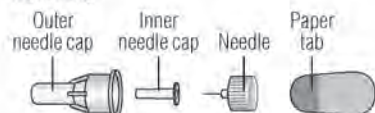
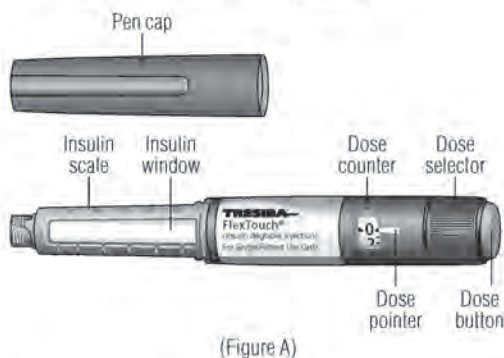
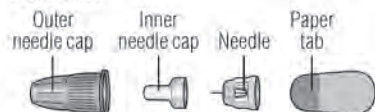
- Do not share your TRESIBA® FlexTouch® Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.
- TRESIBA® FlexTouch® Pen 100 units/mL ("Pen") is a prefilled disposable pen containing 300 units of TRESIBA® (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your TRESIBA® injection:

- TRESIBA® FlexTouch® Pen
- a new NovoFine® or NovoTwist® needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See "After your injection" at the end of these instructions.

Preparing your TRESIBA® FlexTouch® Pen:

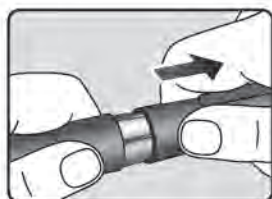
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the TRESIBA® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- TRESIBA® should look clear and colorless. Do not use TRESIBA® if it is cloudy or colored.
- Do not use TRESIBA® past the expiration date printed on the label or 56 days after you start using the Pen.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.

NovoFine®**NovoTwist®**

(Figure A)

Step 1:

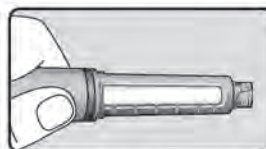
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

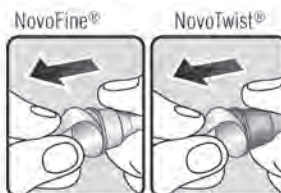
- Check the liquid in the Pen (See Figure C). TRESIBA® should look clear and colorless. Do not use it if it looks cloudy or colored.



(Figure C)

Step 3:

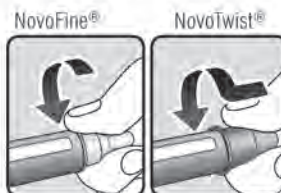
- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

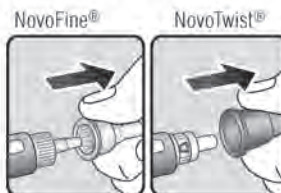
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

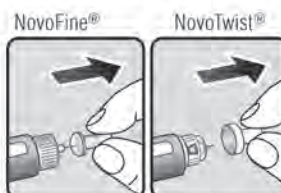
- Pull off the outer needle cap. Do not throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA® FlexTouch® Pen:**Step 7:**

- Turn the dose selector to select 2 units (See Figure H).



(Figure H)

Step 8:

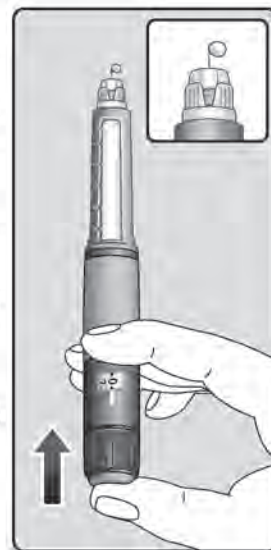
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

Step 9:

- Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
 - If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
 - If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.



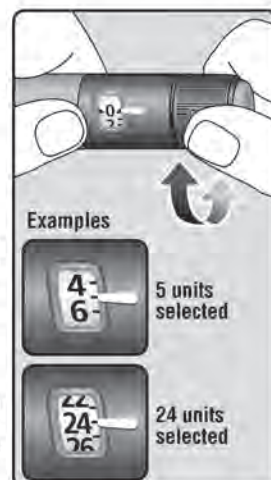
(Figure J)

Selecting your dose:**Step 10:**

TRESIBA® FlexTouch® Pen 100 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. Do not perform any dose conversion.

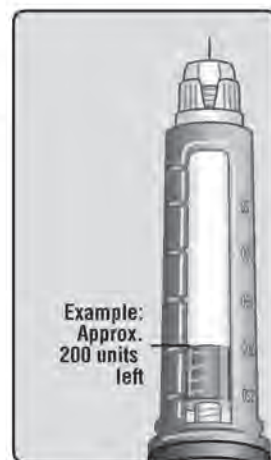
Check to make sure the dose selector is set at 0.

- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
 - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
 - The even numbers are printed on the dial.
 - The odd numbers are shown as lines.



(Figure K)

- The TRESIBA® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

- To see how much insulin is left in your TRESIBA® FlexTouch® Pen:

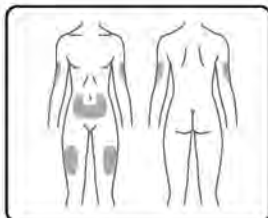
- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are at least 80 units left in your Pen.
- If the dose counter shows less than 80, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your TRESIBA® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA® can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

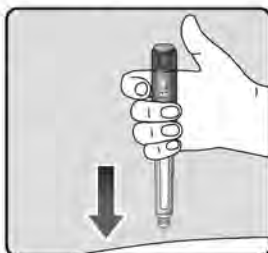
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

Step 12:

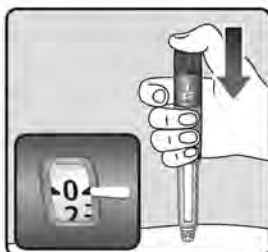
- Insert the needle into your skin** (See Figure N).
 - Make sure you can see the dose counter.** Do not cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

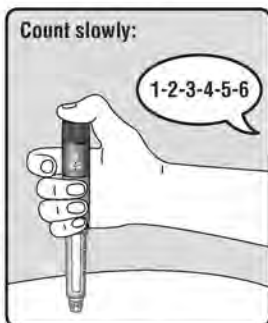
- Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
 - The "0" must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

- Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6** (See Figure P).

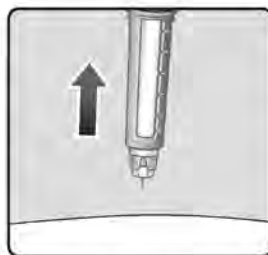
- When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
- If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
- If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



(Figure P)

Step 14:

- Pull the needle out of your skin** (See Figure Q).
 - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

Step 15:

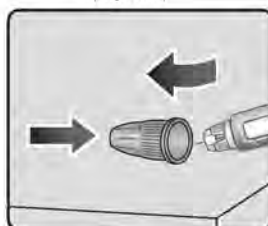
- Carefully remove the needle from the Pen and throw it away** (See Figure R).
 - Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

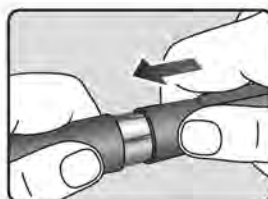
- Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.



(Figure S)

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used TRESIBA® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my TRESIBA® FlexTouch® Pen?**Before use:**

- Store unused TRESIBA® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not** freeze TRESIBA®. **Do not** use TRESIBA® if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA®.

- Keep TRESIBA® FlexTouch® Pens and needles out of the reach of children.**
- Always** use a new needle for each injection.
- Do not** share TRESIBA® FlexTouch® Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 12/2016

For more information go to
www.TRESIBA.com

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USA18TSM01155 April 2018



TRESIBA[®] FLEXTOUCH[®]

How to start and convert your adult patients to once-daily, long-acting Tresiba[®] A basal insulin

Step 1: Initiate¹

Add Tresiba[®] FlexTouch[®]



Form/Strength:

100 units/mL

Quantity per box:

15 mL (5 x 3 mL)

1500 units total

NDC: **0169-2660-15**



Form/Strength:

200 units/mL

Quantity per box:

**9 mL (3 x 3 mL)
1800 units total**

NDC:

0169-2550-13

Below FPG target

-2
units

Within FPG target

0
units

Above FPG target

+2
units

Prescription	Additional Diagnoses	Education
Drug Name	Tresiba® (insulin degludec injection)	
Strength:	200 units/mL solution (subcutaneous) 100 units/mL solution (subcutaneous)	
Dose	Starting dose: 10 units once daily (use as directed)	

Prescribing Tresiba®

When sending prescribing information, be sure to specify the right formulation of Tresiba® for your patients. The U-100 formulation has a maximum dose of 80 units per injection and is dosed in 1-unit increments, and U-200 has a maximum dose of 160 units per injection and is dosed in 2-unit increments.

Also be sure to include:

- Starting dose (units per day)
- Titration information
- Separate prescription for pen needles (if necessary)

Find resources for you and your patients



Eligible patients pay as little as \$15 per prescription^b

[Help patients save](#)



See what to do when patients miss their scheduled dose of Tresiba[®]

[Find guidance](#)

^bFor up to 24 months. Maximum savings of \$500 per prescription. [Eligibility and other restrictions apply.](#)

Selected Important Safety Information

Contraindications

- Tresiba[®] is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to Tresiba[®] or one of its excipients

Warnings and Precautions

- **Never Share a Tresiba[®] FlexTouch[®] Pen Between Patients, even if the needle is changed.** Sharing poses a risk for transmission of blood-borne pathogens
- Monitor blood glucose in all patients treated with insulin. Changes in insulin may affect glycemic control. These changes should be made cautiously and under medical supervision. Adjustments in concomitant anti-diabetic treatment may be needed
- Hypoglycemia is the most common adverse reaction of insulin, including Tresiba[®], and may be life-threatening

Indications and Usage

Tresiba® (insulin degludec injection) is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

Tresiba® is not recommended for treating diabetic ketoacidosis or for pediatric patients requiring less than 5 units of Tresiba®.

Important Safety Information

Contraindications

- Tresiba® is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to Tresiba® or one of its excipients

Warnings and Precautions

- **Never Share a Tresiba® FlexTouch® Pen Between Patients, even if the needle is changed.** Sharing poses a risk for transmission of blood-borne pathogens
- Monitor blood glucose in all patients treated with insulin. Changes in insulin may affect glycemic control. These changes should be made cautiously and under medical supervision. Adjustments in concomitant anti-diabetic treatment may be needed
- Hypoglycemia is the most common adverse reaction of insulin, including Tresiba®, and may be life-threatening. Increase monitoring with changes to: insulin dose, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with hypoglycemia unawareness or renal or hepatic impairment
- Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, always instruct patients to check the insulin label before each injection
- Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Tresiba®
- As with all insulins, Tresiba® use can lead to life-threatening hypokalemia, which then may cause respiratory paralysis, ventricular arrhythmia, and death. Closely monitor potassium levels in patients at risk of hypokalemia and treat if indicated
- Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Tresiba®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered

Adverse Reactions

- Adverse reactions commonly associated with Tresiba® are hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain

Drug Interactions

- There are certain drugs that may cause clinically significant drug interactions with Tresiba[®].
 - o Drugs that may increase the risk of hypoglycemia: antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlinitide, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors
 - o Drugs that may decrease the blood glucose lowering effect: atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones
 - o Drugs that may increase or decrease the blood glucose lowering effect: alcohol, beta-blockers, clonidine, lithium salts, and pentamidine
 - o Drugs that may blunt the signs and symptoms of hypoglycemia: beta-blockers, clonidine, guanethidine, and reserpine

Please [click here](#) for Prescribing Information.

References:

1. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc; December 2016.
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. *Diabetes Care*. 2015;38(1):140-149.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. *Endocr Pract*. 2017;23(2):207-238.
4. Philis-Tsimikas A, Brod M, Niemeyer M, Ocampo Francisco AM, Rothman J. *Adv Ther*. 2013;30(6):607-622.

TOUJEO (too JAY o)

Toujeo Solostar pens contain insulin glargine (Lantus) in a stronger concentration than Lantus. The normal Lantus Solostar uses U-100 insulin, meaning there is 100 units of insulin per ml or cc or the 1.0 mark on a syringe.

The **Toujeo** insulin is U-300 insulin so is three times as strong. The idea is that you use a smaller dose of insulin that is absorbed more evenly from the depot where the dose was put. It has a more even profile than Lantus and less hypoglycemia.

Toujeo is not for treating DKA and it is not used in children yet. Never share your pen. Do not take if you are having low blood sugar.

The dose counter on the **Toujeo** is exactly what your provider tells you to take. Since the pen is what makes the calculations for being 3 times stronger, you would not use a syringe for this insulin.

Do not reuse pen needles, and remove the needle from the pen when dosing is done. Do not store with pen needle on the Solostar pen.

Use **Toujeo** at the same time each day. Rotate where you dose within the abdomen or to an arm, upper outer thigh, or upper buttocks can be used. NEVER mix this insulin with any other insulin.

Check your blood sugar regularly to see effects. Remember, the food, exercise, emotions and illness can all effect your glucose levels. It is suggested to not drive or operate heavy equipment until you know the effect that **Toujeo** has.

Side effects: Low blood sugars are possible, severe allergic reactions, low potassium, heart failure if used with TZD's (Actos).

Medication Guide
AFREZZA® (uh-FREZZ-uh)
(insulin human) inhalation powder

Rx Only

What is the most important information I should know about AFREZZA?

AFREZZA can cause serious side effects, including:

- **Sudden lung problems (bronchospasms).** Do not use AFREZZA if you have long-term (chronic) lung problems such as asthma or chronic obstructive pulmonary disease (COPD). Before starting AFREZZA, your healthcare provider will give you a breathing test to check how your lungs are working.

What is AFREZZA?

- AFREZZA is a man-made insulin that is breathed-in through your lungs (inhaled) and is used to control high blood sugar in adults with diabetes mellitus.
- AFREZZA is not for use in place of long-acting insulin. AFREZZA must be used with long-acting insulin in people who have type 1 diabetes mellitus.
- AFREZZA is not for use to treat diabetic ketoacidosis.
- It is not known if AFREZZA is safe and effective for use in people who smoke. AFREZZA is not for use in people who smoke or have recently stopped smoking (less than 6 months).
- It is not known if AFREZZA is safe and effective in children under 18 years of age.

Who should not use AFREZZA?

Do not use AFREZZA if you:

- have chronic lung problems such as asthma or COPD.
- are allergic to regular human insulin or any of the ingredients in AFREZZA. See the end of this Medication Guide for a complete list of ingredients in AFREZZA.

What should I tell my healthcare provider before using AFREZZA?

Before using AFREZZA, tell your healthcare provider about all your medical conditions, including if you:

- have lung problems such as asthma or COPD
- have or have had lung cancer
- are using any inhaled medications
- smoke or have recently stopped smoking
- have kidney or liver problems
- are pregnant, planning to become pregnant, or are breastfeeding. AFREZZA may harm your unborn or breastfeeding baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins or herbal supplements.

Before you start using AFREZZA, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use AFREZZA?

- Read the detailed **Instructions for Use** that comes with your AFREZZA.
- Take AFREZZA exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much AFREZZA to use and when to use it.
- Know the strength of AFREZZA you use. **Do not** change the amount of AFREZZA you use unless your healthcare provider tells you to.
- Take AFREZZA at the beginning of your meal.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.
- **Keep AFREZZA and all medicines out of the reach of children.**

Your dose of AFREZZA may need to change because of:

- Change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What should I avoid while using AFREZZA?

While using AFREZZA do not:

- drive or operate heavy machinery, until you know how AFREZZA affects you
- drink alcohol or use over-the-counter medicines that contain alcohol
- smoke

What are the possible side effects of AFREZZA?

AFREZZA may cause serious side effects that can lead to death, including:

See "What is the most important information I should know about AFREZZA?"

- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
 - dizziness or light-headedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood change, hunger.
- **decreased lung function.** Your healthcare provider should check how your lungs are working before you start using AFREZZA, 6 months after you start using it and yearly after that.
- **lung cancer.** In studies of AFREZZA in people with diabetes, lung cancer occurred in a few more people who were taking AFREZZA than in people who were taking other diabetes medications. There were too few cases to know if lung cancer was related to AFREZZA. If you have lung cancer, you and your healthcare provider should decide if you should use AFREZZA.
- **diabetic ketoacidosis.** Talk to your healthcare provider if you have an illness. Your AFREZZA dose or how often you check your blood sugar may need to be changed.
- **severe allergic reaction (whole body reaction).** Get medical help right away if you have any of these signs or symptoms of a severe allergic reaction:
 - a rash over your whole body, trouble breathing, a fast heartbeat, or sweating.
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with AFREZZA may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with AFREZZA. Your healthcare provider should monitor you closely while you are taking TZDs with AFREZZA. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
 - shortness of breath, swelling of your ankles or feet, sudden weight gain.Treatment with TZDs and AFREZZA may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

The most common side effects of AFREZZA include:

- low blood sugar (hypoglycemia), cough, sore throat

These are not all the possible side effects of AFREZZA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 (1-800-332-1088).

General information about the safe and effective use of AFREZZA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AFREZZA for a condition for which it was not prescribed. Do not give AFREZZA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about AFREZZA. If you would like more information, talk with your

healthcare provider. You can ask your pharmacist or healthcare provider for information about AFREZZA that is written for health professionals. For more information, go to www.AFREZZA.com or call sanofi-aventis 1-800-633-1610.

What are the ingredients in AFREZZA?

Active ingredient: human insulin

Inactive ingredients: fumaryl diketopiperazine, polysorbate 80

Manufactured By: MannKind Corporation

AFREZZA® is a registered trademark owned by MannKind Corporation

Patented: <http://www.mannkindcorp.com/our-technology-patent-notices.htm>

MannKind Corporation
Danbury, CT 06810

Distributed by:

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
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INS-MG-SA-OCT14

Insulin Delivery Devices

Insulin Delivery Device Handout. Save time with your new insulin patients and let them know what is available. Print out this handout and give to each patient. Insulin Delivery Choices Advertisement

Insulin Delivery Devices



More and more of our patients are going on insulin as their diabetes needs more control. We are all familiar with using vials and syringes but the chances for error, especially in our older patients is great. A study done by Novo-Nordisk in 1999 showed that medical professionals have a 40% error rate in drawing up doses of less than 10 units in a 1cc syringe. Can you imagine how far off patients could be.

We have multiple choices when it comes to deliver devices, some you have and some you can learn more about.

Syringe choices can make a difference. There are 3/10cc, 1/2 cc and 1 cc sizes and the needles come in 28-31 gauge and different lengths. The choice of a 3/10cc syringe for a patient using 13 units allows the patient to be over 60% more accurate.



Then there are the **Pen Devices**. These offer your patients accuracy, convenience and anywhere use.

There are disposable devices, as well as reusable devices and knowing which one to recommend can make a difference for your patient.

Novo makes the **FlexPens** including Levemir, a near peakless long acting insulin Novolog, a rapid acting insulin and NovoMix 70/30 a combination of both rapid and long acting insulin.

All of these come 5 pens in a box and offer 300 units in each disposable pen. They use pen needles from either NOVO or B-D.



The pens can be kept out of the refrigerator for 30 -35

Sanofi

There is no device currently available for their rapid acting insulin Apidra. The Solostar comes in a box of 5 disposal pens 300 units each. This is a great thing for patients using a low dose as each pen is good for 30 days after opening.



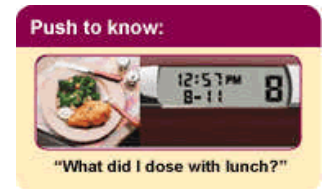
The **Opticlick** pen uses a special cartridge with -
ing phased out by the company.



Eli Lilly has been making their "Turbo" pen for the past 10 years. They still make Humulin N and R as well as Humalog, Humalog 75/25 and Humalog 50/50. Since a lot of our patients are having to pay cash for their insulin the use of Humulin insulins reduces cost.

Memoir. This device uses the 3ml Humalog Cartridge and has a digital readout. Each dose is stored digitally with the time and date when given. The device stores the last 16 doses and is great for patients who are forgetful and might dose twice.

For patients, especially children, who need smaller doses of insulin the **HumaPen Luxura HD** is a great choice. This device uses the same 300 u cartridge and delivers accurate ½ units of insulin. The cartridges come in a box of 5 300u cartridges just like the disposable pens.



The new **KwikPen** is their brand new disposal pen. It is available in Humalog, Humalog 75/25 and Humalog 50/50. This new pen has an easier to read dial, a short throw distance and is a great improvement over the “turbo” pen. The pen is available in boxes of 5 pens with 300 units. Each pen is good for at least 30 day without refrigeration



If your patients want to try any of the **Lilly Pens** have then just go to <http://kwikpenvoucher.humalog.com/voucher.cfm> and print a coupon for a 5 pack.

Pen Needles

All pens need needles and the selection of these are varied as well. The 2 most popular brands are B-D and -
tients but depending on the thickness and density of a patient’s adipose tissue a longer or thicker needle may be necessary.

BD Ultra-Fine needles come in 3 different sizes

- Mini Pen Needle at 5mm and 31 gauge
- Short Pen Needle at 8mm and 31 gauge
- Original Pen Needle at 12.7mm and 29 gauge



NovoFine Disposable Pen Needles come in 2 different sizes

- 31 Gauge x 6 mm
- 30 Gauge x 8 mm

Infusion Ports

Many of our patients use 4-6 injections a day and even more need to increase their injections but don’t want to stick themselves due to the pain or bruising that can occur. For those patients there is the I-Port

altThis device is inserted in the skin every 3 days and then the shot given with a pen or a syringe is given thru the port. So whether it is 3 shots or 5 shots a day the skin is only pierced once every 3 days. To learn more about this device go to <http://www.pattonmd.com/healthcare/>



Little Known Reasons Your Blood Sugar is All Over the Place

Improvements in Injecting Insulin-Part 2



By Joy Pape, MSN, FNP-C, CDE, WOCN, CFCN, FADE

In my [last column](#) I discussed how if you take injectable diabetes meds, your blood sugars can vary for different reasons. For example, it can be the type of diabetes medicine you take, the site you use to inject into, the needle you use, and/or your technique.

Let's take a look at more reasons associated with your site that can cause erratic absorption of insulin.

When you were first taught how to take an insulin injection, you may have been taught to rotate sites. Maybe you weren't or maybe you just got in the habit of injecting one or two places. When you inject in the same place, over time, you may develop one of three types of skin irregularities due to changes in your subcutaneous fat. (1) The three types are:

- Lipohypertrophy. Also known as fat hypertrophy or insulin hypertrophy. "Lipo" stands for fat and the word hypertrophy means excessive growth. Lipohypertrophy looks like "grape-like" lumps under your injection sites. They can feel hard and/or rubbery to touch. It can be caused by insulin itself when repeated injections or insulin at the insulin pump infusion site can cause fat to grow, and by reusing needles.



- Scarring of fat. This appears like the areas of hypertrophy but harder. This can be caused by overusing a site, reusing needles, and at insulin pump infusion sites that are not changed often enough. Fat scarring can be confused with lipohypertrophy, but they are different.
- Lipoatrophy. Also known as fat atrophy. The word "atrophy" means the wasting away of a part of the body. (3) It can be caused by insulin, usually impure insulin like the old beef and pork insulins. We don't see it as often now that we have purer insulins, but it can happen with these and at insulin pump sites. (4) It appears as a loss of fat or "dips or dimples" in your skin and has a firm, not soft bouncy texture as it should.



Some people choose to keep injecting insulin in these sites because the sites are usually less painful or it's just become a habit to inject in these areas. Using these sites or sometimes using them causes glucose variability because, depending where you inject, there can be different absorption of insulin, and different blood glucose levels. What you get is the unexpected blood sugar roller coaster.

Remember, these problems are caused by many factors. Some you have control over, some you don't:

1. How long you've been injecting insulin. The longer you have been injecting, the higher your risk. Not controllable.
2. Not rotating insulin injection sites. Using the same site over and over can increase your risk. Controllable.
3. How often you change your needles. Reusing needles can increase your risk. Controllable.
4. Not changing your infusion sites often enough. Controllable.
5. Using impure insulins. Controllable.

Recommendations to Prevent These Problems

- Feel your sites before you inject, to avoid injecting into these problem areas, unless otherwise instructed by your diabetes health care professional.
- Use all 4 injection sites:
 - Abdomen
 - Arm
 - Thigh

-Buttocks

- Use a larger site "surface" areas, and change to a new site each week
- Rotate injections within each site by 1 centimeter (about ½ inch) between each injection
- Use a new needle each time you inject
- If you wear a pump, follow the above recommendations and change your site more frequently
- Use pure insulins, such as human and/or insulin analogs as prescribed by your diabetes health care professional

Stay tuned for more to come about little-known reasons that could be causing your blood sugar to be all over the place.

If you have been using sites which have lipohypertrophy, scars, or lipoatrophy, to inject into, and decide to switch injection sites, talk with your diabetes health care team to find out if you need to change the amount of insulin you take since you may have better absorption.

When Did I Take Insulin?

Tracking insulin injections decreases risk of lows



By Bennet Dunlap

Starting insulin injections can be stressful. Life has a way of making things routine and [injecting insulin](#) can become one. In many ways, that is a good thing. Getting into the habit of taking insulin regularly can help keep diabetes in check. As taking insulin becomes routine, it is more difficult to remember. Not remembering how much or when insulin was taken can lead to taking too much and dangerous lows can be the outcome.

Insulin is taken to cover food and correct for high blood sugar. Often people do both at the same time. Insulin takes time to lower blood sugar. If you eat more [carbohydrates](#), more insulin is needed to cover that additional food. The last blood sugar correction may still be working and so an additional correction may not be needed, depending on how recently the correction was taken. A correction on top of a still working correction is called "stacking insulin."

Stacking may lead to a risky low blood sugar.

When insulin injections become habit, it is more possible to stack insulin simply as a matter of routine and forgetting when that last injection was. There are tools that can help you remember.

Understanding safe insulin practices and professional help in choosing the right tools for your life style are critical. Like most issues with diabetes, the most important first step is good education. So talk with your diabetes educator about how to avoid stacking insulin.

[Insulin pump](#) users very likely have an algorithm to track insulin on board or IOB. These pump calculations typically reduce suggested insulin doses to account for IOB. Your pump trainer or support team can help you understand the details of how to make the most of insulin on board calculations.

Most people who take insulin do not use pumps. They inject with syringes or pens. Some pens have electronic memory to track the last dose. The NovoPen Echo is one option that is available in the United States. Pens are a more popular choice around the world and more options are available in other countries. These include pens by Lilly and Timesulin's timer cap that fits onto insulin existing pens. Accu-Chek offers insulin injection patients the Aviva

Expert meter that combines blood sugar measurement with the IOB tracking and bolus calculating similar to what is offered in pumps.



There is technology that can help remember when and how much insulin was injected to help support a successful diabetes management routine. If you think one may help you, start by talking with you care professional to better understand the options available and how they may complement your lifestyle.

[Read Bennet's bio here.](#)

[Read more of Bennet's columns.](#)

NOTE: The information is not intended to be a replacement or substitute for consultation with a qualified medical professional or for professional medical advice related to diabetes or another medical condition. Please contact your physician or medical professional with any questions and concerns about your medical condition.

Last Modified Date: June 18, 2014

FRIO® Facts

- ~Keeps insulin cool and safe
- ~Ice packs or refrigeration NOT needed - just activate with water!
- ~Light and compact
- ~Perfect for power outages
- ~Reusable (a very green product)
- ~Perfect for travel. TSA Friendly!
- ~Comes in six colors
- ~Sizes for vials, pens or pumps
- ~Great in **HOT** weather!!! FRIOs® have been used in temperatures in excess of 120°F with complete success.
- ~Tests prove FRIOs® keep contents at around 78°F (25°C) for a minimum of two days in temps of 100°F (38°C). When over 100°F, soak more frequently.
- ~FRIOs® provide insulation, helping to protect insulin from freezing at cold temps.
- ~Low Cost!!!
- ~FRIO® offers convenience, freedom and most importantly, peace of mind!



Scan to view
our Website!

**Activates
with
Water!**



Pump

With FRIO® you have
**Freedom
to Travel the World!**

www.FRIOCase.com



Duo

Resellers Welcome

FRIO®

distributed by

ReadyCare, LLC

1301 Ramsay Circle
Walnut Creek, CA 94597

(925) 937-5288

(888) 909-7737

FRIO® Insulin Cooling Cases

*No Ice Packs...
Ever Again!*



**Convenience,
Freedom &
Peace of Mind**

www.FRIOCase.com

FRIO® Cooling Case

The FRIO® Cooling Case will improve the life of anyone dependent on insulin or many other temperature-sensitive medications.

The FRIO® is a reusable evaporative cooler whose cooling properties do not come from an icepack - or anything that needs refrigeration. Its cooling properties come from the evaporation of water. When activated, it keeps its low temperature for a minimum of two days, even in temperatures of 100°F.

For a FRIO® to be activated, simply soak it in water for 5-10 minutes. It retains its cooling properties for a minimum of two full days. After that, re-soak it in water and it is good for another two days - and so on, and so on...

While a traditional medication cooling case gives you a six to eight hour "chain" to refrigeration, FRIO® cuts that chain. The FRIO® offers the security of not being dependent on refrigeration for the life-critical cooling of your insulin.* It gives you freedom and flexibility to enjoy life as you choose.

Furthermore, because you do not need an icepack or the surrounding insulating materials, the FRIO® wallet is lighter and smaller than traditional medication-cooling cases. There are various sizes of FRIO® available - some small enough to fit in your jean pocket!

PERFECT FOR

*Emergency Kits
Camping & Bike Trips
Working Outdoors
Picnics & Theme Parks
Travel & Daily Use*

These make great gifts!



Large

These are some examples of how the FRIO® will change your life...

Travel~ When you travel, you need to find a way to re-freeze a traditional cooling case throughout the day or overnight. Although many hotels have in-room refrigerators/freezers, many do not. With the FRIO®, you need not worry if there is a refrigerator. All you need is water! The FRIO® is TSA friendly.

Camping~ With a traditional cooling case, camping or backpacking becomes difficult or even impossible. After soaking your FRIO® in water, you can go on a full two-day trip. As long as there is water, the trip can be as long as you want it to be - with no worries!

Confidentiality & Convenience~ It is difficult to maintain confidentiality when you need to take out a large carrying case. You can carry a smaller-sized FRIO® in your pocket. The confidentiality and convenience are both a welcome difference.

Safety ~ After the hurricanes in New Orleans, there were people with Diabetes that died - because of the lack of electricity. Without electricity, there was no refrigeration. Traditional cases could not be kept cool - and insulin went bad. FRIO® users had no such issues. With a FRIO®, you are no longer dependent on ice packs or refrigeration.*

The FRIO® is a basic necessity for the emergency preparedness of anyone using temperature-sensitive medication such as Insulin, Byetta or Victoza.



Individual

FRIO® Products

Mini ~ 3" x 4"
1 vial

Individual ~ 2.5" x 7"
1 pen

Extra Small/ Eye Drop ~ 5" x 5"
3 vials or eye drop bottles

Small ~ 5.5" x 6"
4 vials

Duo ~ 3.25" x 7"
2 pens or 2 vials

Large ~ 5.5" x 7.5"
Up to 4 pens/vials or combo

Extra Large ~ 6" x 8.25"
Up to 8 pens/vials or combo

Pump ~ 3.75" x 4.75"
Comes w/liner. Holds most pumps.

Other FRIO® Products Available:

Head/Neck Coolers
Wrist Bands
Ankle Bands
Migra Head Soothers
Drink Coolers

Available Colors

Black Green
Blue Purple
Burgundy Red



(Head/Wrist/Ankle Bands & Pump not available in Red)

**Insulin to be stored beyond 30 days should be refrigerated
Belts, Pens & Vials not included*

ACTIVATES WITH WATER!

REUSABLE!

www.FRIOCase.com

Beware of Illegally Sold Diabetes Treatments

As the number of people diagnosed with diabetes continues to grow, illegally sold products promising to prevent, treat, and even cure diabetes are flooding the marketplace.

The Food and Drug Administration (FDA) is advising consumers not to use such products. They may contain harmful ingredients or may be otherwise unsafe, or may improperly be marketed as over-the-counter (OTC) products when they should be marketed as prescription products. They carry an additional risk if they cause consumers to delay or discontinue effective treatments for diabetes. Without proper disease management, people with diabetes are at a greater risk for developing serious health complications.

"People with chronic or incurable diseases may feel desperate and become easy prey. Bogus products for diabetes are particularly troubling because there are effective options available to help manage this serious disease rather than exposing patients to unproven and risky products," said Gary Coody, R.Ph., national health fraud coordinator for FDA. "Failure to follow well-established treatment plans can lead to, among other things, amputations, kidney disease, blindness and death."



***Sound too good to be true? Then it's probably a scam.
Watch out for these and similar red flags:***

-  *"Lowers your blood sugar naturally!"*
-  *"Inexpensive therapy to fight and eliminate type II diabetes!"*
-  *"Protects your eyes, kidneys, and blood vessels from damage!"*
-  *"Replaces your diabetes medicine!"*
-  *"Effective treatment to relieve all symptoms of diabetes!"*

Warning Letters Issued

Recently, FDA launched an initiative to counter these illegally sold products aimed at consumers who have diabetes. In addition to evaluating numerous consumer complaints, FDA surveyed the marketplace for illegally sold products promising to treat diabetes and its complications.

In July 2013, FDA issued letters warning 15 companies about selling products for diabetes in violation of federal law. These products are sold as dietary supplements; alternative medicines, such as ayurvedics; prescription drugs and over-the-counter drugs, including homeopathic products. Examples of claims observed on these illegally marketed products include:

- "Lower your blood sugar naturally."
- "Lowers A1C levels significantly."
- "You'll lower your chances of having eye disease, kidney disease, nerve damage and heart disease!"
- "It can replace medicine in the treatment of diabetes."
- "For Relief of Diabetic Foot Pain."

Some of the companies also promote unapproved products for other serious diseases, including cancer, sexually transmitted diseases, and macular degeneration.

FDA tested products marketed as "all natural" treatments for diabetes and discovered some of them contained one or more active ingredients found in prescription drugs to treat type 2 diabetes.

Undeclared ingredients can cause serious harm. If consumers and their health care professionals are unaware of the actual ingredients in the products they are taking, these products may interact in dangerous ways with other medications. One possible complication: Patients may end up taking a larger combined dose of the diabetic drugs than they intended, and that may cause a significant unsafe drop in blood sugar levels, a condition known

as hypoglycemia.

FDA also looked at sales of prescription drugs from fraudulent online pharmacies. Signs that indicate an online pharmacy is legitimate include: requiring that patients have a valid prescription; providing a physical address in the U.S.; being licensed by a state pharmacy board; and having a state-licensed pharmacist to answer questions. Some fraudulent online pharmacies illegally sell drugs that are not approved in the United States, or sell prescription drug products without meeting necessary requirements.

One website that is subject to a warning letter shipped a prescription diabetes drug without requiring a prescription, and even included an unsolicited free sample of a prescription drug for erectile dysfunction. Moreover, the prescription diabetes drug was dispensed without the medication guide and other precautions required by FDA to ensure the drug is used safely and appropriately.

Although some of these websites may offer for sale what appear to be FDA-approved prescription drugs, FDA cannot confirm that the manufacture or the handling of these drugs follows U.S. regulations or that the drugs are safe and effective for their intended uses. Also, there is a risk the drugs may be counterfeit, contaminated, expired or otherwise unsafe.

A Far-Reaching Problem

There are 26 million people in the U.S. who have diabetes, including about 7 million who are undiagnosed, according to the Centers for Disease Control and Prevention. Millions more have pre-diabetes, meaning they have higher than normal blood sugar levels and can reduce their risks of developing diabetes through healthy lifestyle changes, including diet and exercise.

"Products that promise an easy fix might be alluring, but consumers are gambling with their health. In gen-

eral, diabetes is a chronic disease, but it is manageable and people can lower their risk for developing complications by following treatments prescribed by health care professionals, carefully monitoring blood sugar levels, and sticking to an appropriate diet and exercise program," said Coody.

Health care professionals and consumers are encouraged to report any adverse events related to products intended to treat or cure diabetes to FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- online at www.fda.gov/Medwatch/report.htm;
- by phone at 800-FDA-1088 (800-332-1088); or,
- by returning FDA form 3500, available on the MedWatch "Download Forms" page (www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm) by mail to the address on the pre-addressed form or by fax at 800-FDA-0178.

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SAVING MONEY ON MEDICINE

Many drug companies offer diabetes pills or diabetes medicine you inject at low prices or for free to people who cannot afford their medicine. A number of low-cost generic diabetes drugs are also available.

If you cannot afford your diabetes drug, talk to your doctor or pharmacist about a generic drug or call the phone number below that is next to the medicine you take.



LOW-COST GENERIC DIABETES DRUGS

- Pioglitazone (Actos)
- Glimepiride (Amaryl)
- Metformin (Glucophage)
- Glipizide (Glucotrol)
- Glyburide (Micronase)
- Prepaglinide (Prandin)
- Acarbose (Precose)
- Nateglinide (Starlix)

The best generic drug prices are often at nationwide pharmacies, such as CVS or Walgreens, or large chain store pharmacies like those at Walmart and Target.

PATIENT ASSISTANCE PROGRAMS

DIABETES TABLETS

Phone Number

Company

Avandia (rosiglitazone)

1-866-475-3678

Glaxo

Januvia (sitagliptin)

1-800-727-5400

Merck

Invokana (canagliflozin)

1-800-652-6227

Janssen

Farxiga (dapagliflozin)

1-800-736-0003

BMS

Onglyza (saxagliptin)

1-800-292-6363

AstraZeneca

Tradjenta (linagliptin)

1-800-556-8317

Boehringer Ingel.

MEDICINE YOU INJECT

Byetta; Symlin; Bydureon

1-800-303-7647

AstraZeneca

Humalog; Humalog 75/25
Humalog 50-50; Humulin R
Humulin N; Humulin 70-30

1-800-545-6962

Eli Lilly & Co.

NovoLog; NovoLog 70/30
Novolin 70/30; Novolin R
Novolin N; Levemir; Victoza

1-866-310-7549

Novo Nordisk

Lantus; Apidra

1-888-847-8477

Sanofi-Aventis



Not all diabetes medicines are listed.

POSSIBLE DRUG INTERACTIONS

This table lists common blood-glucose-lowering drugs and a number of other drugs (and a food and a supplement) with which they may interact. (Note, however, that this table is not comprehensive.)

COMMON DIABETES MEDICINES	DRUGS THAT CAN INCREASE THE CONCENTRATION OF THIS DIABETES MEDICINE IN THE BLOOD	DRUGS THAT CAN DECREASE THE CONCENTRATION OF THIS DIABETES MEDICINE IN THE BLOOD	OTHER DRUGS AFFECTED BY THIS DIABETES MEDICINE
insulin			Increased risk of fluid retention and heart failure when taken with pioglitazone or rosiglitazone.
metformin (Glucophage, Glucophage XR; also found in Avandamet, Glucovance, Metaglip)	cimetidine nifedipine		Metformin can decrease blood levels of furosemide.
nateglinide (Starlix)	amiodarone cimetidine clarithromycin erythromycin fluconazole fluvastatin grapefruit juice itraconazole ketoconazole lovastatin nefazodone sulfamethoxazole	carbamazepine phenytoin rifampin St. John's wort	Nateglinide may inhibit the metabolism of tolbutamide.
pioglitazone (Actos)	amiodarone cimetidine clarithromycin erythromycin gemfibrozil grapefruit juice itraconazole ketoconazole nefazodone trimethoprim	carbamazepine phenytoin rifampin St. John's wort	Pioglitazone can decrease blood concentrations of amlodipine, atorvastatin, diltiazem, felodipine, lovastatin, nifedipine, nisoldipine, nitrendipine, repaglinide, simvastatin, and verapamil. Also, there is an increased risk of fluid retention and heart failure when taken with insulin.
repaglinide (Prandin)	amiodarone cimetidine clarithromycin erythromycin gemfibrozil grapefruit juice itraconazole ketoconazole nefazodone pioglitazone rosiglitazone trimethoprim	carbamazepine phenytoin rifampin St. John's wort	

COMMON DIABETES MEDICINES	DRUGS THAT CAN INCREASE THE CONCENTRATION OF THIS DIABETES MEDICINE IN THE BLOOD	DRUGS THAT CAN DECREASE THE CONCENTRATION OF THIS DIABETES MEDICINE IN THE BLOOD	OTHER DRUGS AFFECTED BY THIS DIABETES MEDICINE
rosiglitazone (Avandia; also found in Avandamet)	amiodarone fluconazole fluvastatin gemfibrozil lovastatin sulfamethoxazole trimethoprim	rifampin	Rosiglitazone can decrease blood concentrations of amlodipine, atorvastatin, diltiazem, felodipine, lovastatin, nifedipine, nisoldipine, nitrendipine, repaglinide, simvastatin, and verapamil. Also, there is an increased risk of fluid retention and heart failure when taken with insulin.
sulfonylureas: glimepiride (Amaryl), glipizide (Glucotrol, Glucotrol XL; also found in Metaglip), glyburide (DiaBeta, Gly-nase, Micronase; also found in Glucovance), tolbutamide (Orinase)	amiodarone fluconazole fluvastatin lovastatin sulfamethoxazole	rifampin	

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Glucose Sensing Sponge Delivers Insulin Precisely When and Where Needed

Posted By [Editors](#) On July 17, 2013 @ 1:08 pm In [in the news...](#) | [Comments Disabled](#)

Though synthetic insulin and blood glucose meters have been available for decades, diabetics continue experiencing abnormal sugar levels because it's almost impossible to continuously monitor glucose and inject insulin in real-time with sufficient precision. Wearable glucose meters and insulin pumps are currently being investigated to work together as an "artificial pancreas," but there seems to be a limit to how fast changes in blood sugar can be detected and proper insulin dosages delivered.

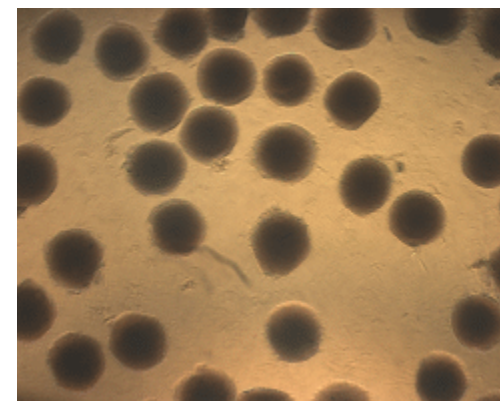
Now a collaboration between North Carolina State University, University of North Carolina at Chapel Hill, MIT, and Boston Children's Hospital has developed and is analyzing a new material that can encapsulate insulin and release it as needed into the blood stream. Made of chitosan, a substance often found in the shells of crustaceans, with a bit of chemical trickery the material expands in the presence of high concentrations of glucose, allowing insulin to flow out and immediately counteract the sugar rush. As glucose levels return to normal, the sponge-like material contracts and stops the flow of insulin. This technique essentially replicates the functionality of β -cells within the pancreas, but further research needs to confirm the safety and efficacy of this technology within diabetic patients. Moreover, the technique allows for other therapeutic compounds to be delivered in response to certain biomarkers, potentially allowing for more targeted treatment of cancer and other diseases.



More details from North Carolina State:

The researchers created a spherical, sponge-like matrix out of chitosan, a material found in shrimp and crab shells. Scattered throughout this matrix are smaller nanocapsules made of a porous polymer that contain glucose oxidase or catalase enzymes. The sponge-like matrix surrounds a reservoir that contains insulin. The entire matrix sphere is approximately 250 micrometers in diameter and can be injected into a patient.

As the insulin is released, the body's glucose levels begin to drop. This causes the chitosan to lose its positive charge, and the strands begin to come back together. This shrinks the size of the pores in the sponge, trapping the remaining insulin. When a diabetic patient's blood sugar rises, the glucose



triggers a reaction that causes the nanocapsules' enzymes to release hydrogen ions. Those ions bind to the molecular strands of the chitosan sponge, giving them a positive charge. The positively charged chitosan strands then push away from each other, creating larger gaps in the sponge's pores that allow the insulin to escape into the bloodstream. In type 1 and advanced type 2 diabetes, the body needs injections of insulin, a hormone that transports glucose – or blood sugar – from the bloodstream into the body's cells.

In this image, the "smart sponges" are exposed to high glucose levels and are swelling to release insulin. Image: Zhen Gu

While this work created hydrogen ions by using enzymes that are responsive to glucose, the technique could be simplified to target cancers by eliminating the enzymes altogether. Tumors are acidic environments that have high concentrations of hydrogen ions. If the sponge reservoir were filled with anticancer drugs, the drugs would be released when the chitosan came into contact with the hydrogen ions in tumor tissues or cancer cells.

Study in *ACS Nano*: [Glucose-Responsive Microgels Integrated with Enzyme Nanocapsules for Closed-Loop Insulin Delivery](#) ^[1]

NC State: [Injectable 'Smart Sponge' Holds Promise for Controlled Drug Delivery](#) ^[2]

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URLs in this post:

[1] Glucose-Responsive Microgels Integrated with Enzyme Nanocapsules for Closed-Loop Insulin Delivery:

<http://pubs.acs.org/doi/abs/10.1021/nn401617u?prevSearch=%255BContrib%253A%2BZhen%2BGu%255D&searchHistoryKey=>

[2] Injectable 'Smart Sponge' Holds Promise for Controlled Drug Delivery: <http://news.ncsu.edu/releases/wms-gu-sponge-2013/>

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Report: FDA comfortable with EMA's diabetes conclusions

July 31 2013

Regulatory concern that diabetes medications known as incretin mimetics could be linked to pancreatic cancer may have eased a bit. Trade publication *BioCentury* is [reporting](#) that the FDA “concurs” with the European Medicines Agency that the medications and disease are not linked. The EMA's Committee for Medicinal Products for Human Use [announced July 26](#) that “presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.” The drugs in question include GLP-1 inhibitors like Novo Nordisk's Victoza, as well as DPP-IV drugs like Merck's Januvia.

The FDA was not able to confirm the report at press time. [UPDATE: The FDA's Center for Drug Evaluation and Research tells *MM&M* that the regulator and the EMA had been in touch regarding the EMA's analyses, and says “our general view is that their conclusions are consistent with our current understanding of the data.” CDER says the FDA also says the current GLP-1 labels reflect “the extent of our understanding of the safety signals at this point in time.” The FDA's GLP-1 study is ongoing, and CDER says an epidemiological study is also in the works.]

CHMP's issue was that the data which appeared to indicate a link had limitations and an underlying potential for bias, as well as differences in age, gender and disease duration among the test subjects, all of which the regulator wrote “preclude a meaningful interpretation of the results.”

ISI Group analyst Mark Schoenebaum told *MM&M* at the time that the read-through in terms of the potential impact this decision could have on the US was unclear, but that it wasn't a bad thing. In a July 26 investor note, he called the concern a “\$3 hole” in Merck shares, and wrote today that *BioCentury*'s news makes him consider “this overhang as largely dead.”

Merck's Tuesday Q2 earnings call did not indicate any concern about the EMA's scrutiny, or even its recent conclusion that fear surrounding DPP-IVs was overrated. In fact, sales of the Januvia and Janumet rose during the quarter, before the EMA weighed in. Further, Merck noted that generics don't pose a threat to these DPP-IVs because these drugs are generally used as a second-line treatment for patients who aren't able to adequately control their condition with cheaper metformin.

The lack of a clear financial impact should not be surprising -- [the American Diabetes Association told MM&M in March that it had not been flooded with patient calls](#). Leerink Swann analyst Seamus Fernandez was also unperturbed by the report, writing in February "we are skeptical that this study alone will have any meaningful impact on use of these therapies."

Search

THE TIMESULIN PEN CAP – A SIMPLE SOLUTION TO A BIG PROBLEM, “WHEN DID I LAST TAKE MY INSULIN?”

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summary: A crowdfunding success brings @Timesulin, an insulin pen dose timing cap, to the US, selling at \$34.99

[Timesulin](#), a pen cap to help patients remember how long it's been since their last dose of insulin, is now available in the US after [raising an impressive \\$36,189 from a crowdfunding campaign](#). This is welcome news for patients on injections and comes after Timesulin's popularity in 40 other countries. Anyone interested can [visit this link](#) to purchase the Timesulin cap, which costs \$34.99 (free shipping in the US) and comes with a 30-day money back guarantee. Timesulin fits all major disposable insulin pens, including the Novo Nordisk Flexpen and [FlexTouch](#), the [Sanofi SoloSTAR](#), and the [Lilly Kwikpen](#).



A highlight of the Timesulin pen cap is the focus on ultra simplicity – the timer is built right into the pen cap, and it begins counting once a patient places the cap back on the insulin pen. It's easy to quickly see how long it's been since the last dose of insulin (i.e., the screen shows the clock and nothing else). After removing the cap, taking a dose of insulin, and putting it back on the pen, the clock resets to zero. The timer can count up to 100 hours since the last injection. The cap lasts for 12 months before it needs to be replaced, and it does not require charging. For a one-minute video of how Timesulin works, see [its website here](#).

Timesulin solves a very meaningful problem – When did I last inject insulin? – without adding any additional burden to those using it. In 2013, a [Novo Nordisk study](#) suggested one in three people living with diabetes skip or incorrectly take an insulin dose three times per month, and that 77% of healthcare providers estimated this number was closer to six times per month. Novo Nordisk has [also posted this nice infographic](#) on the problems with insulin dose timing, citing as many as 93% of people with diabetes have problems remembering the timing of their insulin dosing. Timesulin's approach may help many patients remember to take their

insulin, as well as avoid dangerous insulin “stacking” (taking too many doses too close to each other) that contributes to hypoglycemia. -AB

- See more at: <http://diatribe.org/timesulin-pen-cap-simple-solution-big-problem-when-did-i-last-take-my->

[insulin?utm_source=diaTribe&utm_campaign=e1239ab4cf-](http://diatribe.org/timesulin-pen-cap-simple-solution-big-problem-when-did-i-last-take-my-insulin?utm_source=diaTribe&utm_campaign=e1239ab4cf-)

[diaTribe_Issue_85&utm_medium=email&utm_term=0_75cdadd67f-e1239ab4cf-411726697#sthash.YL5wImO4.dpuf](http://diatribe.org/timesulin-pen-cap-simple-solution-big-problem-when-did-i-last-take-my-insulin?utm_source=diaTribe&utm_campaign=e1239ab4cf-diaTribe_Issue_85&utm_medium=email&utm_term=0_75cdadd67f-e1239ab4cf-411726697#sthash.YL5wImO4.dpuf)

<https://www.companionmedical.com/inpen/#j4mxtg-accordion>



Smart Insulin Delivery
inpen[®]

InPen

A reusable injector pen plus an intuitive smartphone interface equals smart insulin delivery. Simplify your diabetes care plan.



The Pen

The InPen insulin injector pen. An easy-to-use pen that not only helps calculate your doses but also keeps track of injection data.

When paired via **Bluetooth®** with the smartphone app, the InPen delivery system keeps tabs on how many units you received at your last injection, when you took them, and other helpful information.

InPen was designed for insulin-dependent individuals 12 and older undergoing multiple daily subcutaneous injections. It can deliver 0.5 to 30 units of insulin, dialed in half-unit increments. Dial too many units? Not a problem. InPen lets you correct the dose without wasting insulin.

The InPen injector pen is compatible with Lilly Humalog® and Novo Nordisk Novolog® U-100 3.0 mL insulin cartridges and single-use detachable and disposable needles (not included).

InPen is as easy to maintain as it is to use. The InPen lasts for one year – no recharging needed. And with options in blue, grey, and pink, you can even add a bit of color to your management plan.

The App

The InPen app is the other half of InPen's smart diabetes management tool. Using information transmitted from the pen, the app can track insulin therapy, calculate doses, share therapy data with your doctor or family, and much more.

Reports

PDF

Report Period (Days)

7

30

90

Avg. Rapid-Acting Dose	5.9 U
Avg. Rapid-Acting Doses per Day	7.8
Average Total Daily Dose	45.6 U
Average Blood Glucose	159.4 mg/dL
Highest Blood Glucose	365 mg/dL
Lowest Blood Glucose	62 mg/dL
Average Carbohydrates per Meal	47.6 grams
Average Carbohydrates per Day	164 grams
Dose Calculator Usage	82.9 %
Dose Calculator Override	25 %
Average Dose Calculator Override	1 U
Average Meal Reminders per Day	1.1
Average Days per Cartridge	12 days
InPen Life Remaining	<11 months



Home



Logbook



Reports



Settings

Reporting

Reporting lets you easily share your therapy summary with your care providers so you always see the big picture when adjusting your care plan.

InPen is compatible with all Apple iOS devices that support **iOS 10** or greater.

An Android version of the app will be coming soon.

Easy to use and install. The tutorial will walk you through it and a handy link to the online user guide makes sure you're always supported. [Click here](#) to go to the app store.

[Watch a Video](#)

The InPen Smart Insulin Delivery System is now available.

Visit the [Get InPen page](#) to start the process.

Stay Updated...

Sign up for our mailing list to receive periodic company updates on the InPen via email. Your information is of the utmost importance to us and always kept confidential. It is never shared.



Brought to you by your diabetes educator and



Drugs That Can Affect Blood Glucose Levels

Drugs That May Cause Hyperglycemia (High Blood Sugar)

Generic Name	Brand Name
Abacavir	Ziagen®
Abacavir + lamivudine, zidovudine	Trizivir®
Acetazolamide	Diamox®
Acitretin	Soriatane®
Albuterol	Ventolin®, Proventil®
Albuterol + ipratropium	Combivent®
Ammonium chloride	
Amphotericin B	Amphocin®, Fungizone®
Amphotericin B lipid formulations (IV)	Abelcet®
Amprenavir	Agenerase
Aripiprazole	Abilify®
Arsenic trioxide	Trisenox®
Asparaginase	Elspar®
Atenolol + chlorthalidone	Tenoretic®
Atovaquone	Mepron®
Baclofen	Lioresal®
Betamethasone (topical)	Alphatrex®, Betatrex®, Beta-Val®, Diprolene®, Diprolene® AF, Diprolene® Lotion, Luxiq®, Maxivate®
Betamethasone + clotrimazole	Lotrisone® (topical)
Betaxolol	Betoptic® (eyedrops), KERLONE® (oral)
Bexarotene	Targretin®
Bicalutamide	Casodex®
Benazepril + hydrochlorothiazide	Lotension®
Bisoprolol + hydrochlorothiazide	Ziac®
Bumetanide	Bumex®
Caffeine	
Candesartan + hydrochlorothiazide	Atacand HCT®
Captopril + hydrochlorothiazide	Capozide®
Carteolol	Cartrol® (oral), Occupress® (eyedrops)
Carvedilol	Coreg®
Chlorothiazide	Diuril®
Chlorthalidone	Chlorthalidone Tablets®, Clorpres®, Tenoretic®, Thalitone®
Choline salicylate	Numerous tradenames of aspirin formulations; check label
Choline salicylate + magnesium salicylate	CMT®, Tricosal®, Trilisate®
Clobetasol	Clobevate®, Cormax®, Cormax® Scalp Application, Embeline® E, Olux®, Temovate®, Temovate® E, Temovate® Scalp Application
Clozapine	Clozaril®, FazaClo®

Conjugated estrogens	Estrace®, Estring®, Femring®, Premarin®, Vagifem®, Cenestin®, Enjuvia®, Estrace®, Femtrace®, Gynodiol®, Menest®, Ogen®
Conjugated estrogens + medroxyprogesterone	Premphase®, Prempro®
Cyclosporine	Sandimmune®, Neoral®, Gengraf®
Corticotropin	
Cortisone	Numerous tradenames; check label.
Corticosteroids	Numerous tradenames; check label.
Daclizumab	Zenapax®
Desonide	DesOwen®, Tridesilon®
Desoximetasone	Topicort®
Dexamethasone	Adrenocot®, Dalalone®, Decadron®, Decaject®, Dekasol®, Dexacort®, Dexasone®, Dexim®, Dexone®, Hexadrol®, Medidex®, Primethasone®, Solurex®, Dexamethasone Intensol®
Dextromethorphan + promethazine	Phenergan® with Dextromethorphan, Phen-TussDM®
Diazoxide	Proglycem®
Enalapril + hydrochlorothiazide	Vaseretic®
Encainide	Enkaid®
Esterified estrogens, estrone, estropipate	
Esterified estrogens + methyltestosterone	Estrate®
Estradiol, ethinyl estradiol	Alora® Climara® Congest® Delestrogen® Depo-Estradiol® Depogen® Estinyl® Estrace® Estraderm®, Estragyn 5®, Estragyn LA 5®, Estrasorb®, EstroGel®, Estro-L.A.®, Gynodiol®, Kestron-5®, Neo-Estrone® Menest®, Menostar®, Ogen .625® Ogen®, Ortho-Est®, Premarin®, Valergen®, Vivelle®, Vivelle-Dot®
Estradiol + norethindrone	Activella®
Estradiol + norgestimate	Prefest®
Estramustine	Emcyt®
Ethacrynic acid	Edecrin®, Sodium Edecrin®
Fluoxetine	Prozac®, Sarafem®
Flurandrenolide	Cordran®, Cordran® SP, Cordran® Tape
Formoterol	Foradil® Aerolizer® Inhaler
Fosinopril + hydrochlorothiazide	Monopril HCT®
Furosemide	Lasix®
Gatifloxacin	Tequin®, Tequin® Injection, Tequin® Injection Premixed, Zymar® (eyedrops)
Gemtuzumab ozogamicin	Mylotarg®
Hydrochlorothiazide	Aldactazide®, Aldoril®, Capozide®, Dyazide®, HydroDIURIL®, Inderide®, Lopressor® HCT, Maxzide®, Microzide®, Moduretic®, Timolide®, Vaseretic®
Hydrochlorothiazide + irbesartan	Avalide®

Hydrochlorothiazide + lisinopril	Prinzide®, Zestoretic®
Hydrochlorothiazide + losartan	Hyzaar®
Hydrochlorothiazide + metoprolol	Lopressor HCT®
Hydrochlorothiazide + moexipril	Uniretic®
Hydrochlorothiazide + quinapril	Accuretic®, Quinaretic®
Hydrochlorothiazide + telmisartan	Micardis HCT®
Hydrochlorothiazide + valsartan	Diovan HCT®
Hydrocortisone	Numerous tradenames of topical hydrocortisone formulations; check label
Indapamide	Lozol®
Indinavir	Crixivan®
Interferon alfa-2a	Roferon-A®
Interferon alfa-2b	Intron-A®
Interferon alfa-2b + ribavirin	Rebetron®
Interferon alfa-n1	Alferon-N®
Irinotecan	Camptosar®
Isoniazid	Laniazid®, Nydrazid®
Isotretinoin	Accutane®
Lamivudine	Epivir®, Epivir-HBV®
Levalbuterol	Xopenex®, Xopenex HFA®
Levonorgestrel	Plan B®, NORPLANT System®
Lopinavir + ritonavir	Kaletra®
Magnesium salicylate	Bayer Select® Backache Pain Formula, Doans® Pills, Mobidin®, Nuprin® Backache Caplet
Medroxyprogesterone	Provera®, Depo-Provera®
Megestrol	Megace®
Methylprednisolone	A-methaPred®, ADD-Vantage®, Depo-Medrol®, Medrol®, Medrol® Dosepak, Meprolone® Unipak, Solu-Medrol®
Metolazone	Zaroxolyn®, Mykrox®
Metoprolol	Lopressor®, Lopressor® HCT, Toprol XL®
Modafinil	Provigil®
Moxifloxacin	Avelox®, Avelox® I.V.
Mycophenolate	CellCept®
Nadolol	Corgard®
Nelfinavir	Viracept®
Niacin, niacinamide	Niacor®, Niaspan®, Nicolar®, Nicotinex®, Slo-Niacin®
Nilutamide	Nilandron®
Nitric oxide	INOmax®
Norethindrone	Aygestin®, Nor-QD®, Micronor®
Norgestrel	Orvette®
Nystatin	Mycostatin®, Nystat-Rx®, Nystop®, Pedi-Dri®
Nystatin + triamcinolone	Dermacomb®, Myco II®, Mycobiotic II®, Mycogen II®, Mycolog II®, Myco-Triacet II®, Mykacet®, Mykacet II®, Mytrex®, Tristatin II®

Octreotide	Sandostatin®, Sandostatin LAR®
Pantoprazole	Protonix®, Protonix® I.V.
Pegaspargase	Oncaspar®
Peginterferon alfa-2b	PEG-Intron®
Pentamidine	Pentam 300®
Phenytoin	Dilantin®, Dilantin-125®, Dilantin Infatabs®, Dilantin Kapseals®, Phenytek®
Prednisolone	AK-Pred®, Blephamide®, Blephamide® Liquifilm®, Econopred® Plus, Inflamase® Forte, Inflamase® Mild, Poly- Pred® Liquifilm®, Pred Forte®, Pred Mild®, Pred-G®, Pred-G® Liquifilm®, Delta-Cortef®, Pediapred®, Prelone®
Prednisone	Prednisone Intensol®, Sterapred®, Sterapred® DS
Progesterone	Prometrium®
Quetiapine	Seroquel®
Risperidone	Risperdal®, Risperdal® M-TAB®
Ritodrine	Yutopar®
Ritonavir	Norvir®
Rituximab	Rituxan®
Saquinavir	Invirase®
Salmeterol	Serevent®, Serevent® Diskus®
Salsalate	Argesic®-SA, Disalcid®, Mono-Gesic®, Salflex®, Salsitab®
Sodium oxybate	Xyrem®
Somatropin	Genotropin®, Genotropin Miniquick®, Humatrope®, Norditropin cartridges®, Norditropin NordiFlex®, Nutropin®, Nutropin AQ®, Saizen®, Serostim®, Zorbtive®
Sotalol	Betapace®, Betapace AF®, Sorine®
Streptozocin	Zanosar®
Tacrolimus	Prograf®, Protopic®
Torsemide	Demadex®, Demadex Oral®
Triamcinolone	Aristocort®, Aristospan®, Asthmacort®, Flutex®, Kenalog®, Tac®, Triacet®
Ursodeoxycholic acid, ursodiol	Actigall®, Urso®
Valproic acid, divalproex sodium	