Get to Know Tresiba®

Please see Important Safety Information throughout and see Prescribing Information following page 28.
MANAGING TYPE 1 DIABETES

Whether you were just diagnosed with type 1 diabetes or will be caring for a child with type 1 diabetes, there are some important things you need to know. One important thing to know is that managing type 1 diabetes involves taking insulin every day to help control blood sugar. With type 1 diabetes, the body makes little or no insulin. To replace the insulin the body can’t make on its own, a health care provider may prescribe a long-acting insulin like Tresiba®. In addition to taking Treiba® and other medications, healthy eating, physical activity, and tracking blood sugar are important parts of managing type 1 diabetes. While it feels like a lot now, things like giving multiple daily injections, making adjustments to diet, and being more physically active will become part of a daily routine.

What is Tresiba®?
• Prescription Tresiba® is a long-acting insulin used to control high blood sugar in adults and children who are 1 year of age and older with diabetes
• Tresiba® is not for people with diabetic ketoacidosis
• 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: 200 units/mL and 100 units/mL

Important Safety Information
Do not share your Tresiba® FlexTouch® 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.
LET’S GET STARTED

This welcome kit has some helpful information to get started on Tresiba®. Any questions about Tresiba® or managing type 1 diabetes should be discussed with a health care provider. Remember to always follow his or her instructions.

Inside this kit:

- Learn the role Tresiba® plays in managing blood sugar
- Read instructions for using Tresiba® U-100 FlexTouch®
- Get a tool to help track blood sugar
- Use the Instant Savings Card to save on Tresiba®

There is also information about Cornerstones4Care®. Designed specifically for people with diabetes and those who care for them, Cornerstones4Care® offers 24/7 access to information, resources, and ongoing communications that provide tips and tools when they are needed the most.

Important Safety Information (cont’d)

Who should not take Tresiba®?
Do not take Tresiba® if you:
- are having an episode of low blood sugar
- are allergic to Tresiba® or any of the ingredients in Tresiba®

INSULIN AND TYPE 1 DIABETES

Insulin is a hormone produced by the pancreas that helps move sugar out of the blood and into the body’s cells, where this sugar is then used for energy. To do this, the pancreas normally releases insulin in 2 ways:

1. A slow, steady flow of insulin released continuously that helps keep blood sugar controlled overnight and between meals (called basal insulin)
2. Short bursts of insulin released when you eat that prevent rises in blood sugar (“spikes”) that occur with meals (called bolus insulin)

To closely mimic the body’s natural basal-bolus insulin patterns, many people with type 1 diabetes take 2 types of insulin—a basal and a bolus.

- Tresiba® is a “basal” insulin taken once daily that provides blood sugar control for a full 24 hours
- A mealtime, or “bolus,” insulin is taken when you eat to help limit the rise (or spike) in blood sugar that happens at mealtime

A “basal-bolus” regimen can provide a full day of insulin coverage.

Understandingly, taking 2 insulins can seem like a lot, especially when taking many injections a day. But remember, “basal-bolus” treatment can be an important part of a type 1 diabetes care plan to help keep blood sugar under control.

Important Safety Information (cont’d)

Who should not take Tresiba®?

Do not take Tresiba® if you:
- are having an episode of low blood sugar
- are allergic to Tresiba® or any of the ingredients in Tresiba®

Please see Important Safety Information throughout and see Prescribing Information following page 28.
WHAT IS TRESIBA®?

Tresiba® is a long-acting insulin proven to control high blood sugar in adults and children as young as 1 year old with type 1 diabetes. Tresiba® provides blood sugar control for a full 24 hours, with proven A1C reduction. Tresiba® releases slow and steady, to closely mimic the body’s long-acting (basal) rate of insulin release.

TRESIBA®—THE LONG-ACTING (BASAL) PART OF YOUR INSULIN TREATMENT

Tresiba® is one part of the basal-bolus combination treatment that your health care provider prescribed. (Bolus, or mealtime insulin, is the other part.) Tresiba® is designed to replace the long-acting (basal) insulin the body can’t make on its own. Tresiba® releases slowly and consistently. Tresiba® helps sugar in the blood get into the body’s cells, where it can be converted into the energy the body needs.

How do I take Tresiba®?

Tresiba® should only be used as instructed by a health care provider. Tresiba® may be taken with or without food. Tresiba® should be taken once daily at the same time each day as instructed by the health care provider. There are some helpful ways to remember to take Tresiba®, like linking it to another daily activity. For instance, some people take their dose after brushing their teeth in the morning. Or when they get home from school. Setting a daily reminder on a computer, phone, tablet, or watch is also a helpful way to remember.

If children miss a dose, call their health care provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of Tresiba®.

Important Safety Information (cont’d)

Who should not take Tresiba® (cont’d)

Before taking Tresiba®, tell your health care 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 health care provider about low blood sugar and how to manage it.

Important Safety Information (cont’d)

How should I take Tresiba®?

- Read the Instructions for Use and take Tresiba® exactly as your health care provider tells you to
- Do not do any conversion of your dose. The dose counter always shows the selected dose in units

Please see Important Safety Information throughout and see Prescribing Information following page 28.
TRESIBA® FLEXTOUCH®

Tresiba® U-100 FlexTouch® comes prefilled with Tresiba®. And it’s ready to use in just a few easy steps. After priming, dial the exact amount of insulin your health care provider prescribed, and inject into your skin by pushing a button.

We understand that for some people, the thought of injecting can be scary. Tresiba® FlexTouch® is recommended for use with NovoFine® Plus 32G Tip, one of the shortest and thinnest needles available. NovoFine® Plus is designed for less pain. In a study, a majority of people using 32G Tip needles experienced little or no pain. Tresiba® FlexTouch® can also be used with NovoTwist® needles.

Once in use, Tresiba® lasts 56 days (8 weeks) with or without refrigeration or until no insulin is left—whichever comes first. After first use, you can take it almost anywhere without having to carry a cooler. Before use (unopened), Tresiba® can be kept until the expiration date printed on the label if it is stored in a refrigerator (36ºF to 46ºF). Always check the expiration date when you get your prescription. After that date, Tresiba® FlexTouch® should be discarded.

In-use Tresiba® can be kept at room temperature (below 86ºF), away from direct heat and light, or refrigerated (36ºF to 46ºF).

Important Safety Information (cont’d)

How should I take Tresiba®? (cont’d)

• Know the type and strength of insulin you take. Do not change the type of insulin you take unless your health care provider tells you to.
• 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 doses

Tresiba® U-100 FlexTouch®

Prefilled with 300 units of Tresiba®
Maximum of 80 units per dose
No push-button extension

Needles are sold separately and may require a prescription in some states.

It is important that you use a new needle every time you inject. Needles should not be reused.

For complete instructions on how to use Tresiba® U-100 FlexTouch® and to get information about Tresiba® U-200 FlexTouch®, see the full Instructions for Use in the Prescribing Information at http://www.novo-pi.com/tresiba.pdf or you can view a demonstration video at tresiba.com.

Important Safety Information (cont’d)

How should I take Tresiba®? (cont’d)

• If children miss a dose of Tresiba®:
  ◦ Call the health care provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of Tresiba®

Please see Important Safety Information throughout and see Prescribing Information following page 28.
HOW DO I USE MY TRESIBA® FLEXTOUCH®?

Over the next few pages, you’ll find detailed instructions for using your Tresiba® U-100 FlexTouch® (insulin degludec injection). Refer back to this section as often as you need, until you are familiar with all the steps.

To watch a video of these instructions and learn how to use your Tresiba® FlexTouch®, go to tresiba.com.

For a free Tresiba® FlexTouch® training session, please call 1-877-246-8910 to speak with a FlexTouch® Specialist from 9 AM to 6 pm (ET) Monday - Friday.

- If you have any questions about taking Tresiba®, be sure to discuss them with your health care provider, and always follow your health care provider’s directions.

Important Safety Information (cont’d)

How should I take Tresiba®? (cont’d)

- Check your blood sugar levels. Ask your health care provider what your blood sugar levels should be and when you should check them.
- Do not reuse or share your needles with other people. You may give them 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.

Please see Important Safety Information throughout and see Prescribing Information following page 28.
HOW TO USE YOUR PREFILLED TRESIBA® FLEXTOUCH® U-100

1. Preparing your Tresiba® FlexTouch® Pen
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.

A. Pull Pen cap straight off.
B. Check the liquid in the Pen. Tresiba® should look clear and colorless. Do not use if it looks cloudy or colored.
C. Select a new needle, and pull off the paper tab from the outer needle cap.
D. Push the capped needle straight onto the Pen and twist the needle on until it is tight.
E. Pull off the outer needle cap. Do not throw it away. Then, pull off the inner needle cap and throw it away.

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.

Do not use Tresiba® past the expiration date printed on the label or 56 days after you start using the Pen.

Please read the Instructions for Use that came with your Tresiba® FlexTouch® for complete instructions.

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.

Do not share your Tresiba® FlexTouch® with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.

Please see Important Safety Information throughout and see Prescribing Information following page 28.
2. Priming your Tresiba® FlexTouch® Pen

A

Turn the dose selector to select 2 units.

B

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.

C

Always prime your Pen before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to high blood sugar.

If you do not see a drop of insulin, repeat steps A to C, no more than 6 times. If you still do not see a drop of insulin, change the needle and repeat steps A to C. If a drop of insulin does not appear, use a new Pen. Always make sure that a drop of insulin appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose counter may move. This may indicate a blocked or damaged needle.

3. Selecting your dose

You can inject from 1 to 80 units in a single injection. If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.

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.

Tresiba® FlexTouch® U-100 is made to deliver the number of insulin units that your health care provider prescribed. Do not perform any dose conversion.

Please see Important Safety Information throughout and see Prescribing Information following page 28.
4. Giving your injection

Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose. Insert the needle into your skin.

Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection. Press and hold down the dose button until the dose counter shows “0.” The “0” must line up with the dose pointer. You may then hear or feel a click. Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6.

Pull the needle out of your skin. 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.

Carefully remove the needle from the Pen and throw it away. Do not recap the needle. Recapping the needle can lead to needle stick injury.

Replace the Pen cap by pushing it straight on.

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.

Refer to page 19 of this booklet for a diagram of injection sites.

Do not recap the needle. Recapping the needle can lead to needle stick injury.

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.

Please see Important Safety Information throughout and see Prescribing Information following page 28.

Put your used Tresiba® FlexTouch® Pen and needles in a FDA-cleared sharps disposable 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 sharps container, carefully slip the needle into the outer needle cap. Safely remove the needle and throw it away as soon as you can.

If you do not have an FDA-cleared sharps disposable container, you may use a household container that is: 1) heavy-duty plastic, 2) can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out, 3) leak-resistant, 4) properly labeled to warn of hazardous waste inside the container.

When your sharps disposable container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposable container. There may be state or local laws about how you should throw away used needles and syringes.
WHERE TO INJECT

Inject your Tresiba® exactly as your health care provider has shown you. Your health care provider should tell you if you need to pinch the skin before injecting.

Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

- Stomach area (abdomen)
- Upper arms
- Upper legs (thighs)

Tresiba® can be injected under the skin (subcutaneously) of your:
- Stomach area (abdomen)
- Upper arms
- Upper legs (thighs)

Please see Important Safety Information throughout and see Prescribing Information following page 28.
HOW TO STORE TRESIBA® FLEXTOUCH®

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:
• In-use Tresiba® can be kept at room temperature (below 86°F), away from direct heat and light, or refrigerated (36°F to 46°F)
• The Tresiba® FlexTouch® Pen you are using should be thrown away in an approved sharps container after 56 days, even if it still has insulin left in it
• Keep Tresiba® away from heat or light

Important Safety Information (cont’d)

What should I avoid while taking Tresiba®?
• Do not drive or operate heavy machinery, until you know how Tresiba® affects you
• Do not 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 be life-threatening, including:

Please see Important Safety Information throughout and see Prescribing Information following page 28.

SAVE ON TRESIBA®

The Tresiba® Instant Savings Card

Pay as little as $15 per prescription, if eligible.∗

With the Tresiba® Instant Savings Card, you pay as little as $15 per prescription for up to 24 months and receive a FREE box of Novo Nordisk needles.† You will also be automatically enrolled in the complimentary Cornerstones4Care® support program. Go to tresiba.com for full program details and eligibility requirements.

Important Safety Information (cont’d)

• Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include anxiety, irritability, mood changes, dizziness, sweating, confusion, and headache
• Low potassium in your blood (hypokalemia)
• Heart failure in some people if taken with thiazolidinediones (TZDs). This can happen even if you have never had heart failure or heart problems. If you already have heart failure, it may get worse while you take TZDs with Tresiba®. Tell your health care 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

• Maximum savings of $500 per prescription.
• Needles are sold separately and may require a prescription in some states.
TYPE 1 SUPPORT AND RESOURCES...FOR TEENS, YOUNG ADULTS, AND CAREGIVERS

Novo Nordisk offers a wide range of type 1 educational resources that cover a wide range of topics.

**Cornerstones4Care®**

*Cornerstones4Care®* offers 24/7 access to information, resources, and ongoing communications that provide tips and tools when they are needed the most. Get free, personalized diabetes support that also includes:

- **The Diabetes Health Coach** — A step-by-step digital coaching tool that is especially helpful for people who have recently been diagnosed with type 1 diabetes. Get a customized plan to help manage type 1 diabetes that includes e-coaching sessions, interactive tracking tools, and other helpful resources
- **Meal Planning Tools** — A way to plan and track meals and create a menu of tasty, diabetes-friendly dishes
- **Interactive Trackers** — Including A1C, weight, and blood sugar tracking tools

Sign up today at [type1.cornerstones4care.com](http://type1.cornerstones4care.com).

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The type 1 diabetes booklet series: My Life, My Diabetes, My Way

Novo Nordisk has partnered with JDRF, a global leader in type 1 diabetes research, to create the “My Life, My Diabetes, My Way” booklet series that gives patients information on topics of interest based on their age, diabetes experience, and challenges they may be facing at different points in their life. This series offers a booklet for everyone, from parents of toddlers to young adults!

**Important Safety Information (cont’d)**

What are the possible side effects of Tresiba®? (cont’d)

*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, or illness.*

**Common side effects may include** 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, or confusion.

Please see Important Safety Information throughout and see Prescribing Information following page 28.
What is Tresiba®?

• Prescription Tresiba® is a long-acting insulin used to control high blood sugar in adults and children who are 1 year of age and older with diabetes

• Tresiba® is not for people with diabetic ketoacidosis

• 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: 200 units/mL and 100 units/mL

Important Safety Information

Do not share your Tresiba® FlexTouch® 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.

Who should not take Tresiba®?

Do not take Tresiba® if you:

• are having an episode of low blood sugar

• are allergic to Tresiba® or any of the ingredients in Tresiba®

Before taking Tresiba®, tell your health care 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

How should I take Tresiba®?

• Read the Instructions for Use and take Tresiba® exactly as your health care provider tells you to

• Do not do any conversion of your dose. The dose counter always shows the selected dose in units

• Know the type and strength of insulin you take unless your health care provider tells you to

• 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 doses

• If children miss a dose of Tresiba®:
  ◦ Call the health care provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of Tresiba®

What should I avoid while taking Tresiba®?

• Do not drive or operate heavy machinery, until you know how Tresiba® affects you

• Do not 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 be life-threatening, including:

• Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include anxiety, irritability, mood changes, dizziness, sweating, confusion, and headache

• Low potassium in your blood (hypokalemia)

• Heart failure in some people if taken with thiazolidinediones (TZDs). This can happen even if you have never had heart failure or heart problems. If you already have heart failure, it may get worse while you take TZDs with Tresiba®. Tell your health care 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

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, or illness.

Common side effects may include 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, or confusion.

Please see Important Safety Information throughout and see Prescribing Information following page 28.
NOTES

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Please see Important Safety Information throughout and see Prescribing Information following page 28.
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 ———
Indications and Usage (1) 12/2016

——— 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 ———
• Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal (2.1, 2.2, 2.3, 2.4).
• Rotate injection sites to reduce the risk of lipodystrophy (2.1).
• Do not dilute or mix with any other insulin or solution (2.1).
• Administer subcutaneously once daily at any time of day (2.2).
• Do NOT perform dose conversion when using the TRESIBA® U-100 or U-200 FlexTouch® pens. The TRESIBA® U-100 and U-200 FlexTouch® pens dose window shows the number of insulin units to be delivered and NO conversion is needed (2.2).

——— DOSAGE FORMS AND STRENGTHS ———
TRESIBA® 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

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 affect glucose metabolism: Adjustment of insulin dosage may be needed; closely monitor blood glucose (7).
• Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2016

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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 type 2 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.
• Train patients on proper use and injection technique before initiating TRESIBA®. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
• 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)].
• DO NOT administer TRESIBA® intravenously, intramuscularly 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 to a syringe for administration [see Warnings and Precautions (5.4)].

2.2 General Dosing Instructions
• 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 is 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)].

2.3 Starting Dose in Insulin Naïve Patients

Type 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 Therapy

Adults 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

TRESIBA® is available as a clear, colorless solution for injection in:
• 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 oral 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 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)].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:
• Hypoglycemia [see Warnings and Precautions (5.3)].
• Hypersensitivity and allergic reactions [see Warnings and Precautions (5.5)].
• Hypokalemia [see Warnings and Precautions (5.6)].

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.

Do not transfer TRESIBA® from the TRESIBA® pen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia [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 if indicated (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.
TRESIBA® (insulin degludec injection)

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. 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 HbA1c 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 HbA1c 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TRESIBA® (n=1102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>23.9%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>11.8%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5.1%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Adult Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TRESIBA® (n=2713)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>12.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>8.8%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

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.

The incidence of hypoglycemia in clinical trials of TRESIBA® and long-acting insulin comparators were observed in clinical trials conducted in adult patients. Severe hypoglycemia in 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).

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.

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 lipolysis (thinning of adipose tissue) and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy [see Dosage and Administration (2.1)]. In the clinical program, lipodystrophy, lipohypertrophy, or lipolysis was reported in 0.3% of patients treated with TRESIBA®.

Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia® on TRESIBA® in Adult Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>OADs*</th>
<th>Insulin</th>
<th>Severe Hypoglycemia</th>
<th>Novo Nordisk Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>E</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>F</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>G</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>H</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>I</td>
<td>+ 1-2</td>
<td>T2DM</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

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, 35.9% of patients who received TRESIBA® once daily were positive for anti-insulin antibodies (IAA) at least once during the studies, including 89.7% that were positive at baseline. In studies of type 2 diabetes patients, 26.0% of patients who received TRESIBA® once daily were positive for AIA at least once during the studies, including 45.4% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underestimated due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper or hypoglycemia.

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®

<table>
<thead>
<tr>
<th>Drugs That May Increase the Risk of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fribates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramipexole, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
<tr>
<td>Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Alcoholic 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.</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
<tr>
<td>Dose increases and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
<tr>
<td>Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

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 higher than those observed in adult male rats at a dose of 0.75 units/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 a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk for miscarriage in 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 embryofetal development in rabbits. Human insulin (NPH insulin) was included as a comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 units/kg/day in rats and 3.3 units/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure at a dose of 0.75 units/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hyperglycemia.

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 (14.1)] a total of 77 (7%) of the 1102 TRESIBA®-treated patients with type 1 diabetes were 65 years old 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 old or older (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.

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 (14.1)] a total of 77 (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. 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 differences 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 recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

12 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-heaxadecanoyl)-γ-Glu des(B30) human insulin). Insulin degludec has a molecular formula of C270H396O136S6 and a molecular weight of 6103.97. It has the following structure:

![Figure 1: Structural Formula of TRESIBA®](image-url)

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 mg/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 mg/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 (ΔGRmax) of a 0.4 units/kg dose of TRESIBA® was 2.0 mg/dL/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 AUCint,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 (tmax). 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 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.

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 reach 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 a single subcutaneous dose of 0.4 units/kg.

Specific Populations

Pediatric-

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.

Geriatric-

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 (CrCl) as follows: >80 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 (AUC0-12,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,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), Suargre-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 bedtime 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 bedtime 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 HbA1c >60 mL/min/1.73m². The mean BMI was approximately 26.3 kg/m².

At week 52, the difference in HbA1c 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 HbA1C 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 26 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

<table>
<thead>
<tr>
<th></th>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRESIBA® + Insulin aspart</td>
<td>Insulin aspart</td>
</tr>
<tr>
<td>HoA (%)</td>
<td>Baseline</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>End of trial</td>
<td>7.3</td>
</tr>
<tr>
<td>Adjusted mean change from baseline*</td>
<td>-0.36</td>
<td>-0.34</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® at the same time each day + Insulin aspart</th>
<th>Insulin aspart</th>
<th>TRESIBA® at alternating times + Insulin aspart</th>
<th>Insulin aspart</th>
<th>Insulin glargine U-100 + Insulin aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoA (%)</td>
<td>Baseline</td>
<td>7.7</td>
<td>Baseline</td>
<td>7.7</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>End of trial</td>
<td>7.3</td>
<td>End of trial</td>
<td>7.3</td>
<td>164</td>
</tr>
<tr>
<td>Adjusted mean change from baseline*</td>
<td>-0.41</td>
<td>-0.40</td>
<td>-0.57</td>
<td>-0.57</td>
<td></td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + Insulin aspart</th>
<th>Insulin detemir + Insulin aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoA (%)</td>
<td>Baseline</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>End of 26 weeks</td>
<td>8.0</td>
</tr>
<tr>
<td>Adjusted mean change from baseline after 26 weeks*</td>
<td>-0.19</td>
<td>-0.34</td>
</tr>
</tbody>
</table>

### 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 Analogue 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 HbA1C 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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + Insulin aspart</th>
<th>Insulin detemir + Insulin aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoA (%)</td>
<td>Baseline</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>End of 26 weeks</td>
<td>8.0</td>
</tr>
<tr>
<td>Adjusted mean change from baseline after 26 weeks*</td>
<td>-0.19</td>
<td>-0.34</td>
</tr>
</tbody>
</table>
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 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 56.4 years and mean duration of diabetes was 10.6 years. 53.9% were male. 66.7% were White, 25.5% 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 HbA1c reduction from baseline between TRESIBA® 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 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)*

<table>
<thead>
<tr>
<th>N</th>
<th>TRESIBA® + OAD(s)*</th>
<th>Insulin glargine U-100 + OAD(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>773</td>
<td>257</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.06</td>
<td>-1.15</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>TRESIBA® - Insulin glargine U-100</td>
<td>0.09 [-0.34; 0.22]</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>51.7%</td>
<td>54.1%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>174</td>
<td>174</td>
</tr>
<tr>
<td>End of trial</td>
<td>106</td>
<td>115</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-68.0</td>
<td>-60.2</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (starting dose)</td>
<td>10 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Mean dose after 2 weeks</td>
<td>56 U</td>
<td>56 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c 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 HbA1c measurement.

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 26-week randomized, open-label, multicenter trial in 88 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 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 or thiazolidinediones 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, 25.5% 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 HbA1c reduction from baseline between TRESIBA® 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 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)*

<table>
<thead>
<tr>
<th>N</th>
<th>TRESIBA® U-200 + Met + DPP-4</th>
<th>Insulin glargine U-100 + Met + DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>228</td>
<td>229</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.84</td>
<td>-1.22</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>TRESIBA® - Insulin glargine U-100</td>
<td>0.04 [-0.11;0.19]</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>52.2%</td>
<td>55.9%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>172</td>
<td>174</td>
</tr>
<tr>
<td>End of trial</td>
<td>106</td>
<td>113</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-71.1</td>
<td>-63.5</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>10 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>59 U</td>
<td>62 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c 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 HbA1c measurement.
### 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)*

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® at the same time each day ± OAD(s)*</th>
<th>TRESIBA® at alternating times ± OAD(s)*</th>
<th>Insulin glargine U-100 ± OAD(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>228</td>
<td>229</td>
<td>230</td>
</tr>
<tr>
<td>HbA1c (%) Baseline</td>
<td>8.4</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.3</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.03</td>
<td>-1.17</td>
<td>-1.21</td>
</tr>
<tr>
<td>Estimated treatment difference (95% CI) TRESIBA® alternating – Insulin glargine U-100</td>
<td>0.04 [-0.12;0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference TRESIBA® alternating – TRESIBA® same</td>
<td>-0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates.

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 agents (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 HbA1c 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**

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + OAD(s)*</th>
<th>Sitagliptin + OAD(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>225</td>
<td>222</td>
</tr>
<tr>
<td>HbA1c (%) Baseline</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.52</td>
<td>-1.09</td>
</tr>
<tr>
<td>Estimated treatment difference (95% CI) TRESIBA® - Sitagliptin</td>
<td>-0.43 [-0.61; -0.24]</td>
<td></td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates.

### 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 15).

#### 16.2 Recommended Storage

Unused TRESIBA® should be stored between 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.

Unopenend FlexTouch® disposable prefilled pen:
- Not in-use (unopened) TRESIBA® disposable prefilled pen should be stored in a refrigerator (36°F to 46°F (2°C to 8°C)) or be kept at room temperature (below 86°F (30°C)) away from direct heat and light. The opened (in-use) TRESIBA® FlexTouch® pen may be used for up to 56 days (8 weeks) after being opened, if it is refrigerated or kept at room temperature.

The storage conditions are summarized in Table 16:

### Table 15: Presentations of TRESIBA®

<table>
<thead>
<tr>
<th>TRESIBA®</th>
<th>Total volume</th>
<th>Concentration</th>
<th>Total units available in presentation</th>
<th>NDC number</th>
<th>Max dose per injection</th>
<th>Dose increment</th>
<th>Package Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 FlexTouch®</td>
<td>3 mL</td>
<td>100 units/ mL</td>
<td>300 Units</td>
<td>0169-2660-15</td>
<td>80 Units</td>
<td>1 Unit</td>
<td>5 pens/pack</td>
</tr>
<tr>
<td>U-200 FlexTouch®</td>
<td>3 mL</td>
<td>200 units/ mL</td>
<td>600 Units</td>
<td>0169-2550-13</td>
<td>160 Units</td>
<td>2 Unit</td>
<td>3 pens/pack</td>
</tr>
</tbody>
</table>

### Table 16: Storage Conditions for TRESIBA® FlexTouch®

<table>
<thead>
<tr>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated (36°F to 46°F (2°C to 8°C))</td>
<td>Room Temperature (below 86°F (30°C))</td>
</tr>
<tr>
<td>Room Temperature (below 86°F (30°C))</td>
<td>Refrigerated (36°F to 46°F (2°C to 8°C))</td>
</tr>
<tr>
<td>3 mL TRESIBA® U-100 FlexTouch® Until expiration date</td>
<td>56 days (8 weeks)</td>
</tr>
<tr>
<td>3 mL TRESIBA® U-200 FlexTouch® Until expiration date</td>
<td>56 days (8 weeks)</td>
</tr>
</tbody>
</table>
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)]. TRESIBA® FlexTouch® pen is available in concentrations of 100 units/mL or 200 units/mL.

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 that when injecting TRESIBA®, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

• If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would not have received any insulin – even though the dose counter has moved from the original dose that was set.

• If the patient did have a blocked or damaged needle, instruct them to change the needle as described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting with a new needle and the Section Preparing your TRESIBA® FlexTouch® Pen. Make sure the patient selects the full dose needed.

If patients routinely do not hold the needle under the skin as recommended, the patient may need to slightly increase the dialed insulin dose to achieve the patient’s glycemic targets.

Instruct patients to not re-use needles. A new needle must be attached before each injection. Reuse of needles increases the risk of blocked needles which may cause under-dosing or overdosing.

Instruct Patients to never use a syringe to remove TRESIBA® from the FlexTouch® disposable insulin prefilled pen.

Administration

TRESIBA® must only be used if the solution is clear and colorless with no particles visible.

Patients must be advised that TRESIBA® must NOT be diluted or mixed with any other insulin or solution [see Dosage and Administration (2.1)].

Management of Hypoglycemia and Handling of Special Situations

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals [see Warnings and Precautions (5.3)].

Refer patients to the TRESIBA® “Patient Information” for additional information about the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia.

Women of Reproductive Potential

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Rx Only

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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:
• have an allergy to TRESIBA® or any of the ingredients in TRESIBA®.

Before taking TRESIBA®, talk to 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®:
  o Take your dose as soon as you remember then continue with your regular dosing schedule.
  o Make sure there are at least 8 hours between your doses.
• If children miss a dose of TRESIBA®:
  o 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:
  o dizziness or light-headedness  o blurred vision  o anxiety, irritability, or mood changes
  o sweating  o slurred speech  o hunger
  o confusion  o shakiness  o headache
  o 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.
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
re-use or share needles with another person. You may
give other people a serious infection, or get a serious
infection from them.

NovoFine®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoTwist®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

Priming your TRESIBA® FlexTouch® Pen:

Step 1:
- Pull Pen cap straight off
(See 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.

Step 3:
- Select a new needle.
- Pull off the paper tab from the outer needle
cap (See Figure D).

Step 4:
- Push the capped needle straight onto
the Pen and twist the needle on until it is
light (See Figure E).

Step 5:
- Pull off the outer needle cap. Do not
throw it away (See Figure F).

Step 6:
- Pull off the inner needle cap and
throw it away (See Figure G).

Step 7:
- Turn the dose selector
to select 2 units
(See 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).

Selecting your dose:

Step 10:
- TRESIBA® FlexTouch® Pen
200 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.

- Each line on the dial
is an even number.

Examples
- 6 units selected
- 24 units selected
- Approx. 400 units left

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.

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.

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.

- 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.

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.

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.
  - 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.

Step 16:
- Replace the Pen cap by pushing it straight on (See 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.

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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Instructions for Use

TRESIBA® 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®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoTwist®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab
- Pen cap

Insulin scale
- Insulin window
- Dose counter
- Dose selector
- Dose pointer
- Dose button

Step 1:
- Pull Pen cap straight off (See 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.

Step 3:
- Select a new needle.
- Pull off the inner needle cap (See Figure D).

Step 4:
- Push the capped needle straight onto the Pen and twist the needle on until it is light (See Figure E).

Step 5:
- Pull off the outer needle cap. Do not throw it away (See Figure F).

Step 6:
- Pull off the inner needle cap and throw it away (See Figure G).

Step 7:
- Turn the dose selector to select 2 units (See 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).

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.

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.
- The TRESIBA® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).

- To see how much insulin is left in your TRESIBA® FlexTouch® Pen:
  - Turn the dose selector until it stops. The dose pointer 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.

Examples
- 4-6 units selected
- 24 units selected
- Example: Approx. 200 units left

(Figure A) (Figure B) (Figure C) (Figure D) (Figure E) (Figure F) (Figure G) (Figure H) (Figure I) (Figure J) (Figure K) (Figure L)
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.

Step 12:
• Insert the needle into your skin (See Figure N).
  o Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.
  o The “0” must line up exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you 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.
  o Do not recap the needle. Recapping the needle can lead to needle stick injury.
  o 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.
  o 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.

Step 13:
• Press and hold down the dose button until the dose counter shows “0” (See Figure O).
  o The “0” must line up with the dose pointer. You may then hear or feel a click.
  o Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6 (See Figure P).
  o When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  o If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
  o 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.

Step 14:
• Pull the needle out of your skin (See Figure Q).
  o 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.
  o 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.

Step 15:
• Carefully remove the needle from the Pen and throw it away (See Figure R).
  o Do not recap the needle. Recapping the needle can lead to needle stick injury.
  o 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.
  o 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.

Step 16:
• Replace the Pen cap by pushing it straight on (See 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:
  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
  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 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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