

Your Helpful Guide for the Type 1 Diabetes Journey



YOUR HELPFUL GUIDE TO THE TYPE 1 DIABETES JOURNEY

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'll need to know. This brochure provides some of this information. It's divided into 3 sections:

- The first section gives a general introduction to type 1 diabetes
- The second section is specifically for caregivers
- The third section is specifically for younger adults

And remember, this is a brief overview. You can always visit the **Cornerstones4Care®** website, type1.cornerstones4care.com, at any time for further information. Now, let's get started!



BEING DIAGNOSED WITH TYPE 1 DIABETES

Having recently received the diagnosis, you might just now be learning about type 1 diabetes. We'll go into more detail on the following pages; but very simply, in type 1 diabetes, the body makes either very little or no insulin, an essential hormone.

For this reason, anyone with type 1 diabetes needs to take insulin every day. This is why your health care provider prescribed a long-acting, injectable insulin as part of a diabetes treatment plan.

Type 1 diabetes requires daily management and care. But don't be overwhelmed!

Along with a health care provider, diabetes care team, and resources such as the **Cornerstones4Care®** website, type1.cornerstones4care.com, this brochure is intended to help guide children or their caregivers on a journey with type 1 diabetes.

WHAT IS TYPE 1 DIABETES?

Whenever someone eats, their body breaks down some of their food into sugar (also called 'glucose'), which travels in their blood.

For someone *without* type 1 diabetes, a hormone called 'insulin' moves this sugar out of their blood and into their cells, where it's used for energy. But in someone *with* type 1 diabetes, their body's immune system mistakenly attacks and destroys certain cells in their pancreas (called 'beta cells') that make insulin.

And so: a person with type 1 diabetes can't make the insulin their body needs. And without insulin, the sugar in their blood can't get into the cells where it's needed. Instead, the sugar stays in their blood and creates 'high blood sugar'. It can even build to dangerous levels, which can cause serious problems.

To replace the insulin their body doesn't make, a person with type 1 diabetes needs to take insulin every day. They also need to make sure they eat the right foods, get enough activity throughout their day, and check their blood sugar as often as their health care provider instructs.

When combined with taking insulin, lifestyle changes can also help keep blood sugar under control. To help manage type 1 diabetes, follow the 4 basics of type 1 diabetes care, which will be introduced in the next pages.



THE 4 BASICS OF TYPE 1 DIABETES CARE

At first, managing type 1 diabetes can seem like a whole extra layer of work. But type 1 diabetes doesn't have to be overwhelming. Caring for it includes 4 basic steps. These are:

- 1 Healthy Eating
- 2 Being Active
- 3 Taking Insulin
- 4 Tracking Blood Sugar





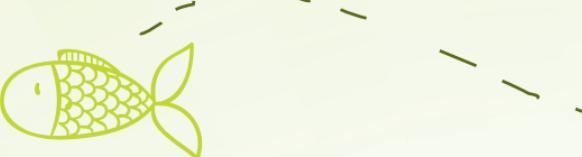
HEALTHY EATING

A person's blood sugar levels are affected by the types and amounts of food they eat. For this reason, it's a good idea to get into the habit of healthy eating.

Maintaining the habit of healthy eating isn't always easy. There will be temptations to eat what friends are eating, or grab a quick bite without thinking. So what does someone with type 1 diabetes need to know to make healthy eating choices, even in not-so-healthy situations?

Well, the basics of healthy eating are the same for people with type 1 diabetes as they are for everyone. Here are some tips:

- Eat regularly, without skipping meals, making sure to track the number of carbohydrates (carbs) eaten during the day (we'll explain carbs at right)
- Trim the fats by choosing low-fat foods, such as fresh fruit, roasted chicken, or baked fish
- Avoid salty snacks, and leave the salt shaker alone



Counting carbs and other nutrients

For someone with type 1 diabetes, healthy eating is all about counting. Reading food nutrition labels can help count:

- Carbohydrate grams (carbs)
- Fat grams
- Sodium milligrams (salt)

Knowing the numbers of carbs in food is important, since carbs tend to raise blood sugar more than other types of food. Generally, simple carbs (sugars) raise blood sugar quickly, while complex carbs (starches) raise blood sugar more slowly. You can find examples of foods with carbs—and find out how to count them—on the **Cornerstones4Care®** website, type1.cornerstones4care.com.

Essentially, the amount of carbs eaten will need to be balanced with how much insulin is taken. Don't worry, though, carbs won't need to be cut out completely, since the body needs carbs for energy, along with essential vitamins and minerals. It's all about balance!



BEING ACTIVE

Whether it's playing sports at school or just playing in the backyard, getting some physical activity into each day can go a long way toward helping manage type 1 diabetes.

Physical activity can give a person more energy. It also makes the body more receptive to insulin, which means less insulin is needed to move sugar out of the blood and into cells.

When someone with type 1 diabetes is physically active, their blood sugar is lowered, so they'll need to take less insulin (or eat more to balance it out). For this reason, be sure to speak with your health care provider about how physical activity can impact a diabetes treatment plan. Here are some important points to remember:

- ➔ **Play it safe.** Be sure to check with your diabetes care team before starting any physical activity or switching to a new activity
- ➔ **Keep it fun.** Choosing a physical activity that's enjoyable is a great way to start. If nothing comes to mind, running or dancing can be good ways to get going



➔ **Check blood sugar.** Before starting any physical activity, it's important to take a blood sugar reading, and avoid getting started if the blood sugar reading is too low (less than 100 mg/dL) or too high (more than 250 mg/dL). Keep in mind, though, blood sugar levels can continue to drop 16 to 24 hours after doing physical activity, since the body is still using the sugar in the blood to replace the sugar used by muscles

➔ **Keep high-sugar "emergency carbs" close at hand.** These can come from fruit juice, glucose tablets, raisins, or hard candies

You can also find more tips on the **Cornerstones4Care®** website, type1.cornerstones4care.com.

★ REMEMBER

Be sure to speak with your health care provider about what to do if blood sugar gets too high or too low. And always follow your health care provider's instructions.



TAKING INSULIN

When someone has type 1 diabetes, their body can't produce the insulin it needs on its own. This is why they need to take insulin by pump or injections every day.

Your health care provider prescribed a long-acting insulin, as well as a fast-acting mealtime insulin. Taking these 2 insulins as instructed can help keep blood sugar in check.

TRACKING BLOOD SUGAR

Since it's inside the body, blood sugar isn't always something that can be "seen". And it's not always something that can be "felt". Checking and tracking blood sugar every day is the only sure way to know how blood sugar is doing, and whether any changes need to be made to the diabetes care plan.

Testing with a blood sugar meter can show how much sugar is in the blood at a particular time. Since food and activity can affect blood sugar levels, blood sugar may need to be checked several times a day.



Your health care team will advise how often and when to check blood sugar. They can also give daily blood sugar goals—a range of numbers that blood sugar should fall within.

The American Diabetes Association (ADA) has its own daily blood sugar and A1C recommendations for people 18 and under. You can find these in the chart below.

SUMMARY OF BLOOD SUGAR GOALS FOR CHILDREN AND TEENS WITH DIABETES (AGES 0-18)	
Before meals (FPG)	90-130 mg/dL
Bedtime/overnight	90-150 mg/dL
A1C	Less than 7.5%

USE A BLOOD SUGAR TRACKER

Blood sugar numbers can be tracked in a diary. We suggest using the one included in this kit. It includes places to write in activities, medications, and useful numbers along with some helpful tips.

A1C—AN IMPORTANT NUMBER TO KNOW

When learning about type 1 diabetes, you'll often hear the term 'A1C', which is a measurement of average blood sugar level over 3 months. An 'A1C test' is done at a health care provider's office. Anyone who has diabetes will have an 'A1C goal'. This number comes from a person's health care provider.

According to the American Diabetes Association (ADA), anyone younger than 18 years of age should aim for an A1C of less than 7.5%. If A1C is higher than goal, the diabetes treatment plan may need to be adjusted.

A1C Goals for Children (ages 0-18)

A1C

Less than 7.5%

Learn more about taking insulin and A1C at the **Cornerstones4Care®** website, type1.cornerstones4care.com.

REMEMBER

It's important to take long-acting insulin along with fast-acting mealtime insulin as instructed by the health care provider. Speak with your health care provider about what to do if a dose is missed or forgotten. Also, keep in mind that low blood sugar can be a side effect of all insulin medicines. To learn more about low blood sugar, see page 19.



WHAT 'A1C' MEANS

When 'glucose' (blood sugar) enters red blood cells, it links with 'hemoglobin' (a protein inside the cells) and becomes 'hemoglobin A1C', or simply, 'A1C'. Red blood cells live about 3 months, so A1C is typically checked every 3 months; this reading is like a "snapshot" of blood sugar levels over that period of time.

FOR CAREGIVERS OF A CHILD WITH TYPE 1 DIABETES

FROM DIAGNOSIS TO ACCEPTANCE

If your child was diagnosed with type 1 diabetes, you need to know—and help your child understand—there's no way to "prevent" type 1 diabetes... it just happens. But, *there is* hope in taking the right kinds of action to care for it.

Instead of letting the future seem overwhelming, you can help an older child understand the control they could have over their care. And your presence can reassure a child of any age that they are *not* alone. With acceptance comes positivity—and strength.



KEEPING IT POSITIVE—IT STARTS AT HOME

Managing type 1 diabetes is an everyday process. It can seem overwhelming at first, for parent and child alike. As you care for your child, stressing the positives can go a long way toward helping them feel okay with their condition.

Here are some suggestions for keeping it positive:

- **Discuss type 1 diabetes.** Oftentimes, the best way to accept something is to discuss it openly. When done together, between you and your child, this can be an exercise in communication. You can also start a conversation about type 1 diabetes with your family, and extend it to your friends. And ultimately, your community.
- **Spend time together.** Blood sugar checks and taking insulin can coincide with regularly scheduled "together times", such as watching movies, doing projects, playing games, or even playing sports.
- **Establish a healthy diet.** This can be the start of eating—even cooking—healthy foods together; after all, the roots of bonding are often planted in the kitchen and at the dinner table. As a parent *and* a caregiver, nurturing a close relationship with your child is important!

And remember: your child's diabetes care team is always available to help *you* as you support your child; and online resources can be great sources of information. You can find a wealth of information on the **Cornerstones4Care®** website, type1.cornerstones4care.com.



CHECKING BLOOD SUGAR & TAKING INSULIN

Daily type 1 diabetes management can be difficult with children.

First of all, try to resist the temptation to become the “diabetes police”. Persuasion can be more effective than scolding—for example, if your child eats too many carbs or sugary snacks. Instead of focusing on the problem, focus on a solution.

Also, practical tasks such as checking blood sugar and taking insulin can be important habits for a child with type 1 diabetes to develop. Just like brushing teeth, these need to be done—even if children tend to resist such “must dos”.

Here are tips for adopting a lighthearted spirit to serious tasks:

- Combine checking blood sugar and taking insulin with fun distractions, like watching a quick video, singing a fun song, or playing an interesting game
- Arrange worrisome-looking supplies (such as lancets!) well out of sight until the last possible moment
- Get to be as much of an expert at checking blood sugar and taking insulin as you can, so these take as little time as possible

You can help your child develop a positive attitude toward a condition they’ll likely need to manage their entire life. As a caregiver and a parent, it’s a great foundation to help build—and a lasting gift to give.



THE HIGHS & LOWS OF BLOOD SUGAR

High blood sugar

High blood sugar ('hyperglycemia') can happen easily in people with type 1 diabetes. So it's important to keep track of your child's blood sugar levels and watch out for physical symptoms, such as:

- ➔ Feeling very thirsty
- ➔ Going to the bathroom to pee more than usual
- ➔ Feeling very hungry
- ➔ Feeling sleepy
- ➔ Blurry vision

Hyperglycemia can be caused by:

- ➔ Accidentally skipping a dose of insulin
- ➔ Eating more than usual
- ➔ Being less active
- ➔ Feeling sick or stressed

If your child has an episode of high blood sugar, be sure to write it down and let their health care provider know immediately. Understanding *why* it happened may help prevent it from happening again.

Low blood sugar

Low blood sugar ('hypoglycemia') can be a side effect of diabetes medicines. So it's a good idea to keep track of your child's blood sugar levels and watch out for physical symptoms, such as:

- ➔ Feeling shaky
- ➔ Feeling sweaty
- ➔ Feeling dizzy
- ➔ Feeling weak or tired
- ➔ Feeling nervous or upset
- ➔ Feeling very hungry
- ➔ Headaches
- ➔ Changes in mood or behavior

Hypoglycemia can occur without symptoms. Be sure to regularly check your child's blood sugar.

The quickest treatment for hypoglycemia is some form of sugar (like pieces of hard candy). It's best to be safe—if your child shows signs of low blood sugar, give them a sugary snack or a glucose tablet. Then, contact their health care provider, or call 911 if their symptoms worsen or persist.

To learn more about the symptoms of high and low blood sugar and how to treat them, you can visit the **Cornerstones4Care®** website, type1.cornerstones4care.com.



IMPORTANT THINGS TO LOOK OUT FOR

DKA (diabetic ketoacidosis)

When the body doesn't have enough insulin to get blood sugar into cells, a dangerous condition known as 'DKA' (diabetic ketoacidosis) can develop. Without blood sugar for energy, the body starts breaking down fats instead. This creates waste products called 'ketones', which can build up and make blood acidic. DKA is very serious, and needs to be addressed *immediately*. So you should know the physical symptoms of DKA, such as:

- ★ Stomach pain
- ★ Difficulty breathing
- ★ Fruity odor on the breath
- ★ Nausea and vomiting



A urine test that detects ketones can be bought at a pharmacy without a prescription.



Nighttime lows

Low blood sugar can occur in the middle of the night. Your child may wake with a headache, have damp sheets from sweating, and/or feel irritable or confused. If this happens, you should speak with your child's health care provider about how to prevent it. Common causes are going to sleep late and having dinner late, as insulin is still lowering their blood sugar.

Passing out

Your child's blood sugar may get so low that it causes them to pass out. If this ever happens, you can give your child an emergency injection of glucagon, which raises their blood sugar instead of lowering it. For this reason, it's important to discuss giving emergency glucagon with your child's health care provider, and always keep emergency glucagon on hand.



IMPORTANT

KEEP A DIABETES EMERGENCY KIT

Type 1 diabetes requires daily maintenance and care. But unforeseen events—such as power outages, blizzards, floods, or hurricanes—can sometimes get in the way. For this reason, it's important to pack a diabetes emergency kit, and keep it ready in case of emergencies.

The American Diabetes Association (ADA) recommends preparing a diabetes emergency kit to last for up to 3 days, if needed. Your diabetes care team can confirm what to include, but an emergency kit should generally include the following:

- ➔ Important medications such as insulin, insulin delivery supplies, and oral medications (remember to refrigerate insulin as needed, and always check expiration dates)
- ➔ Fast-acting carbs to counter blood sugar lows
- ➔ Basic supplies for checking, such as lancets and test strips
- ➔ A spare blood sugar meter, with extra batteries
- ➔ Glucagon for emergency lows
- ➔ A written list of emergency contacts (since a battery failure or power outage can affect your mobile phone)



TIME FOR SCHOOL

Sending a child with type 1 diabetes off to school can feel like sending them off into the wide world. The care they get at home will need to be extended into their new environment. Also, each phase of school will have its own specific needs, from grade school to high school to college. So, be sure to talk with your child's diabetes care team for specific advice during each phase. Here are some tips to create a school care plan:

- ▶ Meet with the school staff to explain your child's type 1 diabetes, and create a diabetes care plan that can ensure their needs are met
- ▶ Ask about Section 504 Plans, which require that the needs of students with disabilities be met; and IEPs (Individualized Education Programs), which are written plans to meet specific learning needs
- ▶ Make sure your child has a diabetes emergency kit (see page 22) always available in their classroom or dorm room
- ▶ Talk with the school guidance counselor or school nurse for updates and advice
- ▶ Take into account any school-related stress, such as exams, peer pressure, and even dating
- ▶ Watch for signs of bullying: having diabetes makes someone "different", and little incidents can add up and make a child feel "blue"



★ REMEMBER

As your child progresses from grade to grade, be sure to stay in touch with their teachers and their diabetes care team.

JDRF

Juvenile Diabetes Research Foundation (JDRF) is the leading global organization funding type 1 diabetes research. You can visit the JDRF website, JDRF.org, and download its School Advisory Toolkit for further suggestions about schooling with type 1 diabetes.



NOT ALWAYS THE ONLY CAREGIVER

There will come a time when you realize that you and your significant other won't always be the only caregivers for your child with type 1 diabetes. The resulting emotions can be similar to letting your child go!

When you're not around, your child's temporary caregivers may become their grandparents or teachers, your friends, their friend's parents, etc. Assigning the tasks of caring for a child with type 1 diabetes can be difficult, but not impossible. All it takes is thought and planning.

Here are some tips:

- ▶ Schedule time to meet and chat with your child's temporary caregiver *before* they're needed, so they can process what needs to be done and ask any necessary questions
- ▶ Explain all the relevant needs: blood sugar checking and insulin taking schedules, signs and symptoms of blood sugar highs and lows, etc.



- ▶ Pack everything that's needed (see the diabetes emergency kit on page 22), and explain each item in detail
- ▶ If an overnight event, explain the symptoms of nighttime lows (see page 21)
- ▶ Provide additional contact numbers, if for some reason you become unreachable
- ▶ Consider using a remote blood glucose monitoring system or app—your child's diabetes care team can give you more information to help you find one



DON'T FORGET TO CARE FOR YOURSELF!

Caring for a child with type 1 diabetes can take a lot of effort, especially if you're not only their caregiver, but *also* their parent. So... don't forget to care for yourself, too!

You might get so involved in caring for your child with type 1 diabetes that you lose sight of your own basic needs. "Caregiver burnout" is an all too common situation. Here are some signs:

- A constant feeling of fatigue
- Less interest in work and activities
- Withdrawing from family and friends
- Increased use of alcohol or stimulants
- Eating more or less than usual
- Feeling overwhelmed or depressed

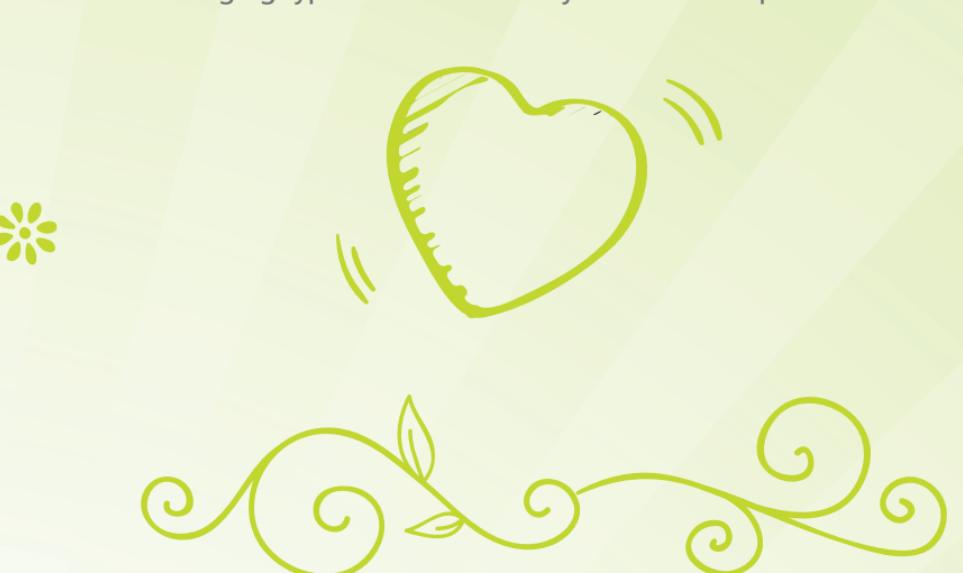
Managing type 1 diabetes is a lifelong journey... for your child *and* for you. It's all about pacing, and not taking on more than you can handle. Good ways to counter caregiver burnout are sharing the responsibilities with family and friends, joining a support group, practicing meditation, or simply taking time for yourself.

A helpful source of support is the **Cornerstones4Care®** website, type1.cornerstones4care.com.

REMEMBER

Don't forget your child's diabetes care team! Just as you help *your child* feel supported, having a support system *for you* can be just as important. By caring for yourself, you can help make sure you'll be able to care for your child for the long term—and even set a positive example for their own future self-care.

When it comes to managing type 1 diabetes... every bit of care helps!



FOR YOUNG ADULTS WITH TYPE 1 DIABETES

TYPE 1 DIABETES... IT CAN BE MANAGED

It can feel a little unsettling to learn you have type 1 diabetes—especially as a teenager, when there's already so much going on in your life. You'll need more help from your parents and other caregivers, when you're probably wanting more freedom.

But it's okay. You can have both.

Since you have type 1 diabetes, your body doesn't produce the insulin it needs to change sugar from the food you eat into energy. For this reason, you need to take insulin by pump or injections every day. This is why your health care provider prescribed a long-acting, injectable insulin as part of your diabetes care plan.

When you have type 1 diabetes, it can take a while to get familiar with everything you'll need to do. Taking insulin every day, counting carbs whenever you eat, and checking your blood sugar regularly may all seem strange at first, but you'll get more used to doing these over time.

And remember, you won't have to do these alone. Your parents, caregivers, and diabetes care team will all want to help. Let them—they can help take some of the pressure off!

REMEMBER

Take it easy on yourself! Every once in a while, you'll eat something that you shouldn't have. Or you'll forget to check your blood sugar. It's okay: a slip-up isn't the end of the world. You can bounce back, pick up your healthy habits, and continue to manage your type 1 diabetes successfully.





HORMONAL CHANGES IN YOUR BODY

As a young person with type 1 diabetes, hormonal changes during puberty and your teen years are probably causing your body to change in ways that aren't within your control.

These changes are normal. But some of them can affect your blood sugar, making it tougher for you to keep it in control. (For example, you may get hungrier than usual.) That's why it's important to stick with your diabetes care plan, eat healthy and stay active, check and track your blood sugar, and take insulin as your health care provider instructs.

If you notice your blood sugar readings are going up or going down, be sure to tell your parents and health care provider immediately. You should also be aware of the signs of symptoms of high and low blood sugar, so you can respond appropriately or ask for help when you need it. You can learn about these on the next pages.



RECOGNIZING HIGH & LOW BLOOD SUGAR

High blood sugar

Your blood sugar can also get too high. High blood sugar ('hyperglycemia') can be caused by:

- Not taking enough insulin
- Eating more than planned

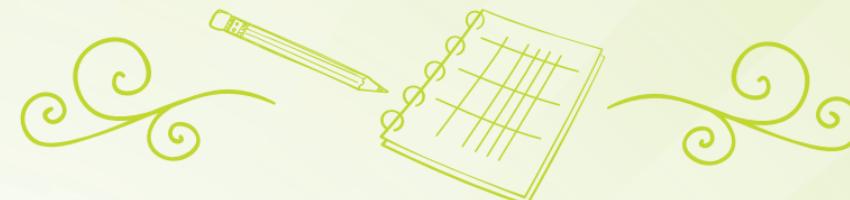
- Being less active than planned
- Having physical or emotional stress (such as from sickness or excitement)

With high blood sugar, you may feel:

- Very thirsty or hungry
- Tired or weak

- Blurry vision
- Having to go to the bathroom to pee more often than usual

If low blood sugar and/or high blood sugar happen to you, be sure to note the day and time in your blood sugar diary, and tell your caregivers, health care provider, and/or diabetes care team as soon as possible. Understanding *why* it happened may help you prevent it from happening again.





Low blood sugar

Low blood sugar ('hypoglycemia') is just what it sounds like—your blood sugar is lower than normal (usually less than 70 mg/dL). Low blood sugar can be caused by:

- ★ Taking too much insulin
- ★ Skipping a meal (or eating later than usual)
- ★ Not eating enough carbohydrates (carbs)
- ★ Too much physical activity

If your blood sugar gets too low, you may have symptoms, such as feeling:

- Weak or tired
- Sweaty
- Hungry
- Your heart is beating too fast
- Dizzy or shaky
- Your vision is getting blurry
- Nervous or upset

The quickest way to treat low blood sugar is by taking some form of sugar, such as fruit juice or hard candies. Many people carry glucose tablets, which you can find at a drugstore without a prescription.



MANAGE TYPE 1 DIABETES... WITH A LITTLE HELP

A big part of growing up with type 1 diabetes is knowing what you can do on your own, versus knowing when to ask for help. It's a balance you'll need to consider as you go along.

Some things you *can* do on your own. Like making decisions to eat certain foods, get outside and stay active, and say to yourself, "I'm going to track my blood sugar and take my insulin as my health care provider told me to."

But it's also important to know that you *do* have help, if you need it. Your parents and caregivers can help. Your health care provider and diabetes care team can help. Even your friends can help—a little support can go a long way!

★ ONLINE SUPPORT

An online Diabetes Health Coach is available at the [Cornerstones4Care®](#) website, type1.cornerstones4care.com. This digital coaching tool is helpful for people who have recently been diagnosed with type 1 diabetes. It offers e-coaching sessions, interactive tracking tools, and other helpful resources to help you build a plan for managing your type 1 diabetes.



Driving with type 1 diabetes

If you have type 1 diabetes and you've already started driving, there are certain things you'll need to do before you get behind the wheel:

- Always check your blood sugar before getting into the car. If your blood sugar isn't within your target range, *don't drive!*
- Pay attention to how you feel. If you feel *any* symptoms of low blood sugar, pull over immediately!
- Avoid eating while driving, as eating can affect your blood sugar while you're on the road, as well as distract your attention

Telling friends about your type 1 diabetes

Telling your friends that you have type 1 diabetes doesn't need to be awkward. You're the same person you were before you were diagnosed. Besides, diabetes is more common than you might think. In fact, some of your friends might already know someone who has diabetes.

Talking to friends about your diabetes might even help. You can tell them how you would feel if you had low or high blood sugar, and explain what they could do if you have an emergency.

Going to parties with type 1 diabetes

Even with type 1 diabetes, you can hang out with your friends and go to parties. You'll just need to do some pre-party planning before you go.

If you just entered your teens, your parents or caregivers will want to speak to your friend's parents, to make sure they know you have type 1 diabetes. If you need help checking your blood sugar or taking your insulin, be sure to ask your parents to show your friend's parents what to do. And, it's definitely a good idea to let them know how to use emergency medicine—called glucagon—in case you get low blood sugar, and for you to carry glucagon with you at all times.

If you're a bit older, you may already be a pro at checking your blood sugar. You may also know what to eat and how to take your insulin. Even so, it's a good idea to tell your friends (and their parents) what to do in case of an emergency. You should also keep the emergency contact list included in this kit on you at all times—and make sure it has contact info for your parents, your caregivers, and key members of your diabetes care team.

Dating with type 1 diabetes

When should you tell your date that you have type 1 diabetes? Every relationship goes at its own pace, and everyone has their own comfort level—but just like talking to your friends, telling your date that you have type 1 diabetes doesn't need to be awkward. You don't have to turn it into a big deal, but you *should* let them know that there are certain things you'll need to do regularly, like taking your insulin and checking your blood sugar.

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

Talk to your health care provider about low blood sugar and how to manage it.

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. **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
- 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®
- **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

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 Prescribing Information following page 40.

TRESIBA®
insulin degludec injection 100 U/mL, 200 U/mL

REMEMBER

For more tips on caring for type 1 diabetes, visit the
Cornerstones4Care® website, type1.cornerstones4care.com.

**Please see Important Safety Information on pages 38 and 39 and
Prescribing Information following page 40.**

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TRESIBA®

insulin degludec injection 100 U/mL, 200 U/mL

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRESIBA® (insulin degludec injection), for subcutaneous use

Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

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 and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that 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

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

TRESIBA® is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended for pediatric patients requiring less than 5 units of TRESIBA®

2 DOSAGE AND ADMINISTRATION**2.1 Important Administration Instructions**

- Always check insulin labels before administration [see Warnings and Precautions (5.4)].
- Inspect visually for particulate matter and discoloration. Only use TRESIBA® if the solution appears clear and colorless.
- 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 into 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)].
- For adult patients, instruct patients who miss a dose of TRESIBA® to inject their daily dose during waking hours upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive TRESIBA® injections.
- For pediatric patients, instruct patients who miss a dose of TRESIBA® to contact their healthcare provider for guidance and to monitor blood glucose levels more frequently until the next scheduled TRESIBA® dose.
- DO NOT perform dose conversion when using the TRESIBA® U-100 or U-200 FlexTouch® pens. **The dose window for both the TRESIBA® U-100 and U-200 FlexTouch® pens shows the number of insulin units to be delivered and NO conversion is needed.**

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, and 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 time course of TRESIBA® may vary among different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see Drug Interactions (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.6, 8.7)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TRESIBA® and other insulins, instruct patients to always check the insulin label before each injection.

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.

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)]

6.1 Clinical Trial Experience

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

The safety of TRESIBA® in subjects with type 1 diabetes or type 2 diabetes was evaluated in nine trials of 6-12 month duration in adults and in one trial of 12-month duration in pediatric patients 1 year of age and older with type 1 diabetes [see Clinical Studies (14)].

The data in Table 1 reflect the exposure of 1102 adults with type 1 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 34 weeks. The mean age was 43 years and 1% were older than 75 years. Fifty-seven percent were male, 81% were White, 2% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 26 kg/m². The mean duration of diabetes was 18 years and the mean HbA_{1c} at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 7% and 0.5% respectively. The mean eGFR at baseline was 87 mL/min/1.73 m² and 7% of the patients had an eGFR less than 60 mL/min/1.73 m².

The data in Table 2 reflect the exposure of 2713 adults with type 2 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 36 weeks. The mean age was 58 years and 3% were older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African American and 13% were Hispanic. The mean BMI was 30 kg/m². The mean duration of diabetes was 11 years and the mean HbA_{1c} at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 14%, 10%, 6% and 0.6% of participants respectively. At baseline, the mean eGFR was 83 mL/min/1.73 m² and 9% had an eGFR less than 60 mL/min/1.73 m².

Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA® treated subjects during clinical trials in adult patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

174 pediatric patients 1 year of age and older with type 1 diabetes were exposed to TRESIBA® with a mean exposure to TRESIBA® of 48 weeks. The mean age was 10 years: 25% were ages 1–5 years, 40% were ages 6–11 years, and 35% were ages 12–17 years. 55.2% were male, 78.2% were White, 2.9% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 18.7 kg/m². The mean duration of diabetes was 3.9 years and the mean HbA_{1c} at baseline was 8.2%. Common adverse reactions in TRESIBA® treated pediatric patients with type 1 diabetes mellitus were similar to the adverse reactions listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Adult Patients with Type 1 Diabetes Mellitus

Adverse Reaction	TRESIBA® (n=1102)
Nasopharyngitis	23.9 %
Upper respiratory tract infection	11.9 %
Headache	11.8 %
Sinusitis	5.1 %
Gastroenteritis	5.1 %

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

Adverse Reaction	TRESIBA® (n=2713)
Nasopharyngitis	12.9 %
Headache	8.8 %
Upper respiratory tract infection	8.4 %
Diarrhea	6.3 %

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TRESIBA® [see Warnings and Precautions (5.3)]. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for TRESIBA® with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

The percentage of adult and pediatric patients with type 1 diabetes randomized to TRESIBA® who experienced at least one episode of hypoglycemia in clinical trials [see Clinical Studies (14)] and adults with type 2 diabetes are shown in Tables 3 and 4, respectively. No clinically important differences in risk of hypoglycemia between 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). A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: Percent (%) of Type 1 Diabetes Patients Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia^{\$} on TRESIBA® in Adult and Pediatric Clinical Trials

	Study A Adults + insulin aspart 52 weeks	Study B Adults + insulin aspart 26 weeks	Study C Adults + insulin aspart 26 weeks	Study J Pediatrics + insulin aspart 52 weeks
TRESIBA® (N=472)	TRESIBA® (N=301)	TRESIBA® at the same time each day (N=165)	TRESIBA® at alternating times (N=164)	TRESIBA® (N=174)
Severe hypoglycemia*				
Percent of patients	12.3%	10.6%	12.7%	10.4%
Novo Nordisk hypoglycemia^{\$}				
Percent of patients	95.6%	93.0%	99.4%	93.9%
*Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy				
\$Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).				

(glucagon or intravenous glucose).

^{\$}Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

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

	Study D + 1-2 OADs* insulin naïve 52 weeks	Study E + 1-2 OADs* insulin naïve 26 weeks	Study F ± 1-3 OADs* insulin naïve 26 weeks	Study G T2DM ± 0-3 OADs* 26 weeks	Study H T2DM ± 0-2 OADs* + insulin aspart 52 weeks	Study I T2DM ± 1-2 OADs* insulin naïve 26 weeks
TRESIBA® (N=766)	TRESIBA® (N=228)	TRESIBA® (N=284)	TRESIBA® (N=226)	TRESIBA® (alternating time) (N=230)	TRESIBA® (N=753)	TRESIBA® (N=226)
Severe Hypoglycemia						
Percent of patients	0.3%	0	0	0.9%	0.4%	4.5%
Novo Nordisk Hypoglycemia^{\$}						
Percent of patients	46.5%	28.5%	50%	43.8%	50.9%	80.9%
*OAD: oral antidiabetic agent, ^{\$} Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).						

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including TRESIBA® and may be life threatening [see Warnings and Precautions (5.5)]. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were reported in 0.9% of patients treated with TRESIBA®.

Lipodystrophy

Long-term use of insulin, including TRESIBA®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect insulin absorption. 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 lipoatrophy was reported in 0.3% of patients treated with TRESIBA®.

Injection Site Reactions

Patients taking TRESIBA® may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass. In the clinical program, injection site reactions occurred in 3.8% of patients treated with TRESIBA®.

Weight Gain

Weight gain can occur with insulin therapy, including TRESIBA®, and has been attributed to the anabolic effects of insulin. In the clinical program after 52 weeks of treatment, patients with type 1 diabetes treated with TRESIBA® gained an average of 1.8 kg and patients with type 2 diabetes treated with TRESIBA® gained an average of 3.0 kg.

Peripheral Edema

Insulin, including TRESIBA®, may cause sodium retention and edema. In the clinical program, peripheral edema occurred in 0.9% of patients with type 1 diabetes mellitus and 3.0% of patients with type 2 diabetes mellitus treated with TRESIBA®.

6.2 Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRESIBA® with the incidence of antibodies in other studies or to other products, may be misleading.

In studies of adult type 1 diabetes patients, 95.9% of patients who received TRESIBA® once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7% that were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received TRESIBA® once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients. The 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®

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA®	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA®	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with TRESIBA® or insulin degludec in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations].

Rats and rabbits were exposed to insulin degludec in animal reproduction studies during organogenesis. Pre-and post-implantation losses and visceral/skeletal abnormalities were observed in rats at doses 5 times (rat) and at 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. These effects were similar to those observed in rats administered human insulin (NPH) [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1c} >7 and has been reported to be as high as 20-25% in women with a HbA_{1c} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. Insulin degludec is present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRESIBA® and any potential adverse effects on the breastfed infant from TRESIBA® or from the underlying maternal condition.

Data

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

8.4 Pediatric Use

The safety and effectiveness of TRESIBA® to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of TRESIBA® have not been established in pediatric patients less than 1 year old.

The use of TRESIBA® in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) [see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]. The use of TRESIBA® in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus [see Clinical Studies (14.3)].

In pediatric patients 1 year of age and older already on insulin therapy, start TRESIBA® at a reduced dose to minimize the risk of hypoglycemia [see Dosage and Administration (2.4)].

8.5 Geriatric Use

In controlled clinical studies [see Clinical Studies (14)] a total of 77 (7%) of the 1102 TRESIBA®-treated patients with type 1 diabetes were 65 years or older and 9 (1%) were 75 years or older. A total of 670 (25%) of the 2713 TRESIBA®-treated patients with type 2 diabetes were 65 years or older and 80 (3%) were 75 years or older. Differences in safety or effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

Nevertheless, greater caution should be exercised when TRESIBA® is administered to geriatric patients since greater sensitivity of some older individuals to the effects of TRESIBA® cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.6 Renal Impairment

In clinical studies [see Clinical Studies (14)] a total of 75 (7%) of the 1102 TRESIBA®-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m² and 1 (0.1%) had an eGFR less than 30 mL/min/1.73 m². A total of 250 (9%) of the 2713 TRESIBA®-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m² and no subjects had an eGFR less than 30 mL/min/1.73 m².

No clinically relevant difference in the pharmacokinetics of TRESIBA® was identified in a study comparing healthy subjects and subjects with renal impairment including subjects with end stage renal disease [see Clinical Pharmacology (12.3)]. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA® dosage adjusted on an individual basis in patients with renal impairment.

8.7 Hepatic Impairment

No difference in the pharmacokinetics of TRESIBA® was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) [see Clinical Pharmacology (12.3)]. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA® dosage adjusted on an individual basis in patients with hepatic impairment.

10 OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia [see Warnings and Precautions (5.3, 5.6)]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

TRESIBA® (insulin degludec injection) is a long-acting basal human insulin analog for subcutaneous injection. Insulin degludec is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecanoyl-γ-Glu) des(B30) human insulin). Insulin degludec has a molecular formula of C₂₇₄H₄₁₁N₆₅O₈₁S₆ and a molecular weight of 6103.97. It has the following structure:

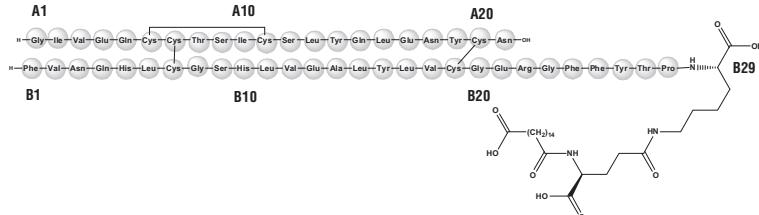


Figure 1: Structural Formula of TRESIBA®

TRESIBA® is a sterile, aqueous, clear, and colorless solution that contains insulin degludec 100 units/mL (U-100) or 200 units/mL (U-200).

Inactive ingredients for the 100 units/mL are: glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 32.7 mcg/mL and water for injection.

Inactive ingredients for the 200 units/mL are: glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 71.9 mcg/mL and water for injection.

TRESIBA® has a pH of approximately 7.6. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including TRESIBA®, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. TRESIBA® forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time

action profile of TRESIBA® is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

12.2 Pharmacodynamics

The glucose-lowering effect of TRESIBA® after 8 days of once-daily dosing was measured in a euglycemic glucose clamp study enrolling 21 patients with type 1 diabetes. Figure 2 shows the pharmacodynamic effect of TRESIBA® over time following 8 once-daily subcutaneous injections of 0.4 U/kg of TRESIBA® in patients with type 1 diabetes.

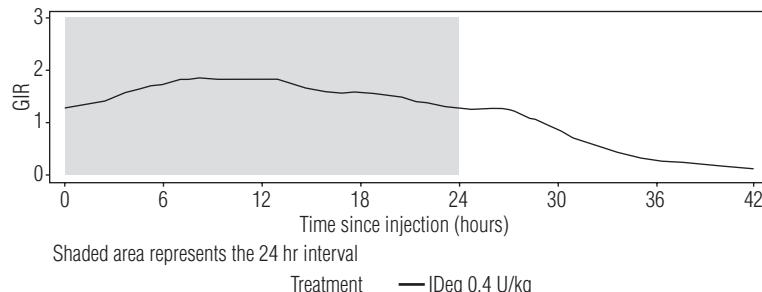


Figure 2: Mean GIR Profile for 0.4 units/kg Dose of TRESIBA® (Steady State) in Patients with Type 1 Diabetes Mellitus

The mean maximum glucose lowering effect (GIR_{max}) of a 0.4 units/kg dose of TRESIBA® was 2.0 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect of TRESIBA® lasted at least 42 hours after the last of 8 once-daily injections.

In patients with type 1 diabetes mellitus, the steady-state, within subjects, day-to-day variability in total glucose lowering effect was 20% with TRESIBA® (within-subject coefficient of variation for $AUC_{GIR,t,ss}$).

The total glucose-lowering effect of TRESIBA® over 24 hours measured in a euglycemic clamp study after 8 days of once-daily administration in patients with type 1 diabetes increases approximately in proportion to the dose for doses between 0.4 units/kg to 0.8 units/kg.

The total glucose-lowering effect of 0.4 units/kg of TRESIBA® U-100 and 0.4 units/kg of TRESIBA® U-200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study after 8 days of once-daily injection was comparable.

12.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 units/kg of TRESIBA®, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (t_{max}). After the first dose of TRESIBA®, median onset of appearance was around one hour.

Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 units/kg to 0.8 units/kg TRESIBA®. Total and maximum insulin degludec exposure at steady state are comparable between TRESIBA® U-100 and TRESIBA® U-200 when each is administered at the same units/kg dose.

Insulin degludec concentration 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 single subcutaneous dose of 0.4 units/kg.

Specific Populations

Pediatrics

Population pharmacokinetic analysis was conducted for TRESIBA® using data from 199 pediatric subjects (1 to <18 years of age) with type 1 diabetes. Body weight was a significant covariate affecting the clearance of TRESIBA®. After adjusting for body weight, the total exposure of TRESIBA® at steady state was independent of age.

Geriatrics

Pharmacokinetic and pharmacodynamic response of TRESIBA® was compared in 13 younger adult (18–35 years) and 14 geriatric (≥65 years) subjects with type 1 diabetes following two 6-day periods of once-daily subcutaneous dosing with 0.4 units/kg dose of TRESIBA® or insulin glargine. On average, the pharmacokinetic and pharmacodynamic properties of TRESIBA® at steady-state were similar in younger adult and geriatric subjects, albeit with greater between subject variability among the geriatric subjects.

Gender

The effect of gender on the pharmacokinetics of TRESIBA® was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA®. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

Obesity

The effect of BMI on the pharmacokinetics of TRESIBA® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA®. For subjects with type 1 diabetes, no relationship between exposure of TRESIBA® and BMI was

observed. For subjects with type 1 and type 2 diabetes a trend for decrease in glucose-lowering effect of TRESIBA® with increasing BMI was observed.

Race and Ethnicity

TRESIBA® has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus conducted using unit/kg doses of TRESIBA®. There were no statistically significant differences in the pharmacokinetic and pharmacodynamic properties of TRESIBA® between the racial and ethnic groups investigated.

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRESIBA® has not been studied [see Use in Specific Populations (8.1)].

Renal Impairment

TRESIBA® pharmacokinetics was studied in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA®. Renal function was defined using creatinine clearance (Cl_{Cr}) as follows: ≥90 mL/min (normal), 60–89 mL/min (mild), 30–59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0-120h,SD}$) 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® ($CL/F_{IDeg,SD}$) in subjects with ESRD [see Use in Specific Populations (8.6)].

Hepatic Impairment

TRESIBA® has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA®. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No differences in the pharmacokinetics of TRESIBA® were identified between healthy subjects and subjects with hepatic impairment [see Use in Specific Populations (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study including human insulin (NPH insulin) as comparator (6.7 units/kg/day), Sprague-Dawley rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 units/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 units/kg/day. Human insulin was dosed at 6.7 units/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. Further, no treatment related changes in the occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when compared to vehicle or human insulin.

Genotoxicity testing of insulin degludec was not performed.

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 units/kg/day (approximately 5 times the human subcutaneous dose of 0.75 units/kg/day, based on units/body surface area) prior to mating and in female rats during gestation had no effect on mating performance and fertility.

14 CLINICAL STUDIES

The efficacy of TRESIBA® administered once-daily either at the same time each day or at any time each day in patients with type 1 diabetes and used in combination with a mealtime insulin was evaluated in three randomized, open-label, treat-to-target, active-controlled trials in adults and one randomized, open-label, treat-to-target, active-controlled trial in pediatric patients 1 year of age and older. The efficacy of TRESIBA® administered once-daily either at the same time each day or at any time each day in adult patients with type 2 diabetes and used in combination with a mealtime insulin or in combination with common oral anti-diabetic agents was evaluated in six randomized, open-label, treat-to-target active-controlled trials.

Adult patients treated with TRESIBA® achieved levels of glycemic control similar to those achieved with LANTUS® (insulin glargin 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 glargin U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 58.5% were male. 93% were White, 1.9% Black or African American. 5.1% were Hispanic. 8.6% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 26.3 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargin U-100 was -0.01% with a 95% confidence interval of [-0.14%; 0.11%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study A.

Study B

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 455 patients with type 1 diabetes mellitus (Study B). Patients were randomized to TRESIBA® or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed twice-daily.

67.1% used insulin detemir once daily at end of trial. 32.9% used insulin detemir twice daily at end of trial. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 13.9 years. 51.9% were male. 44.6% were White, 0.4% Black or African American. 4.4% were Hispanic. 4.4% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 23.9 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin detemir was -0.09% with a 95% confidence interval of [-0.23%; 0.05%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study B.

TABLE 6: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 (Study A) and Week 26 in a Trial Comparing TRESIBA® to Insulin Detemir (Study B) in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	Study A		Study B	
	TRESIBA® + Insulin aspart	Insulin glargine U-100 + Insulin aspart	TRESIBA® + Insulin aspart	Insulin detemir + Insulin aspart
N	472	157	302	153
HbA _{1c} (%)				
Baseline	7.7	7.7	8.0	8.0
End of trial	7.3	7.3	7.3	7.3
Adjusted mean change from baseline*	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference [95%CI] TRESIBA® - basal insulin U-100	-0.01 [-0.14;0.11]		-0.09 [-0.23;0.05]	
Proportion Achieving HbA _{1c} < 7% at Trial End	39.8%	42.7%	41.1%	37.3%
FPG (mg/dL)				
Baseline	165	174	178	171
End of trial	141	149	131	161
Adjusted mean change from baseline	-27.6	-21.6	-43.3	-13.5
Daily basal insulin dose				
Baseline mean	28 U	26 U	22 U	22 U
Mean dose at end of study	29 U ¹	31 U ¹	25 U ²	29 U ²
Daily bolus insulin dose				
Baseline mean	29 U	29 U	28 U	31 U
Mean dose at end of study	32 U ¹	35 U ¹	36 U ²	41 U ²

¹At Week 52

²At Week 26

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

In Study A, there were 14.8% of subjects in the TRESIBA® and 11.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

In Study B, there were 6.3% of subjects in the TRESIBA® and 9.8% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

Study C: TRESIBA® Administered at the Same Time Each Day or at Any Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to TRESIBA® injected once-daily at the same time each day (with the main evening meal), to TRESIBA® injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Insulin aspart was administered before each meal in all treatment arms.

The mean age of the trial population was 43.7 years and mean duration of diabetes was 18.5 years. 57.6% were male. 97.6% were White, 1.8% Black or African American. 3.4% were Hispanic. 7.4% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 26.7 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® administered at alternating times and insulin glargine U-100 was 0.17% with a 95% confidence interval of [0.04%; 0.30%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

Table 7: Results at Week 26 in a Trial Comparing TRESIBA® Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin Glargine U-100 in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA® at the same time each day + Insulin aspart	TRESIBA® at alternating times + Insulin aspart	Insulin glargine U-100 + Insulin aspart
N	165	164	164
HbA _{1c} (%)			
Baseline	7.7	7.7	7.7
End of trial	7.3	7.3	7.1
Adjusted mean change from baseline*	-0.41	-0.40	-0.57
Estimated treatment difference [95%CI] TRESIBA® alternating - Insulin glargine U-100		0.17 [0.04;0.30]	
Proportion Achieving HbA _{1c} < 7% at Trial End	37.0%	37.2%	40.9%
FPG (mg/dL)			
Baseline	179	173	175
End of trial	133	149	151
Adjusted mean change from baseline	-41.8	-24.7	-23.9
Daily basal insulin dose			
Baseline mean	28 U	29 U	29 U
Mean dose at end of study	32 U	36 U	35 U
Daily bolus insulin dose			
Baseline mean	29 U	33 U	32 U
Mean dose at end of study	27 U	30 U	35 U

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study C, there were 15.8% and 15.9% of subjects in the TRESIBA® (same time and alternating times respectively) and 7.9% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

14.2 Type 1 Diabetes – Pediatric Patients 1 Year of Age and Older

Study J: TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Pediatric Patients 1 Year of Age and Older

The efficacy of TRESIBA® was evaluated in a 26-week, randomized, open label, multicenter trial in 350 patients with type 1 diabetes mellitus (Study J). Patients were randomized to TRESIBA® once-daily or insulin detemir once or twice-daily. Subjects on a twice-daily insulin detemir regimen were dosed at breakfast and in the evening either with the main evening meal or at bedtime. Insulin aspart was administered before each main meal in both treatment arms. At end of trial, 36% used insulin detemir once daily and 64% used insulin detemir twice daily.

The mean age of the trial population was 10 years; 24% were ages 1–5 years; 39% were ages 6–11 years and 36% were ages 12–17 years. The mean duration of diabetes was 4 years. 55.4% were male. 74.6% were White, 2.9% Black or African American. 2.9% were Hispanic. The mean z-score for body weight was 0.31.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin detemir was 0.15% with a 95% confidence interval of [-0.03%; 0.33%] and met the pre-specified non-inferiority margin (0.4%). See Table 8.

Table 8: Results at Week 26 in a Trial Comparing TRESIBA® to Insulin Detemir in Pediatric Patients 1 Year of Age and Older with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA® + Insulin aspart	Insulin detemir + Insulin aspart
N	174	176
HbA _{1c} (%)		
Baseline	8.2	8.0
End of 26 weeks	8.0	7.7
Adjusted mean change from baseline after 26 weeks ⁺	-0.19	-0.34
Estimated treatment difference [95%CI] TRESIBA® v. Insulin detemir	0.15 [-0.03; 0.33]	
FPG (mg/dL)		
Baseline	162	151
End of 26 weeks	150	160
Adjusted mean change from baseline after 26 weeks	52.0	59.6
Daily basal insulin dose		
Baseline mean	15 U (0.37 U/kg)	16 U (0.41 U/kg)
Mean dose after 26 weeks	16 U (0.37 U/kg)	22 U (0.51 U/kg)
Daily bolus insulin dose		
Baseline mean	20 U (0.50 U/kg)	20 U (0.52 U/kg)
Mean dose after 26 weeks	23 U (0.56 U/kg)	22 U (0.57 U/kg)

⁺The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with missing data imputed by multiple imputation carrying forward the baseline value and adding the error term, with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate.

In Study J, there were 2.9% of subjects in TRESIBA® and 6.3% Insulin detemir arms for whom data was missing at the 26-week HbA_{1c} measurement.

14.3 Type 2 Diabetes – Adult

Study D: TRESIBA® Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Metformin alone (82.5%) or in combination with a DPP-4 inhibitor (17.5%) was used as background therapy in both treatment arms.

The mean age of the trial population was 59.1 years and mean duration of diabetes was 9.2 years. 61.9% were male, 88.4% were White, 7.1% Black or African American, 17.2% were Hispanic. 9.6% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 31.1 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.09% with a 95% confidence interval of [-0.04%; 0.22%] and met the pre-specified non-inferiority margin (0.4%). See Table 9.

Table 9: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® + OAD(s)*	Insulin glargine U-100 + OAD(s)*
N	773	257
HbA_{1c} (%)		
Baseline	8.2	8.2
End of trial	7.1	7.0
Adjusted mean change from baseline**	-1.06	-1.15
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.09 [-0.04;0.22]	
Proportion Achieving HbA_{1c} < 7% at Trial End	51.7%	54.1%
FPG (mg/dL)		
Baseline	174	174
End of trial	106	115
Adjusted mean change from baseline	-68.0	-60.2
Daily insulin dose		
Baseline mean (starting dose)	10 U	10 U
Mean dose after 52 weeks	56 U	58 U

*ODA: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study D, there were 20.6% of subjects in the TRESIBA® and 22.2% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study E: TRESIBA® U-200 Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA® U-200 was evaluated in a 26-week randomized, open-label, multicenter trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® U-200 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Both treatment arms were receiving metformin alone (84%) or in combination with a DPP-4 inhibitor (16%) as background therapy.

The mean age of the trial population was 57.5 years and mean duration of diabetes was 8.2 years. 53.2% were male, 78.3% were White, 13.8% Black or African American, 7.9% were Hispanic. 7.5% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 32.4 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® U-200 and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.11%; 0.19%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

Table 10: Results at Week 26 in a Trial Comparing TRESIBA® U-200 to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® U-200 + Met ± DPP-4	Insulin glargine U-100 + Met ± DPP-4
N	228	229
HbA_{1c} (%)		
Baseline	8.3	8.2
End of trial	7.0	6.9
Adjusted mean change from baseline**	-1.18	-1.22
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.04 [-0.11;0.19]	
Proportion Achieving HbA_{1c} < 7% at Trial End	52.2%	55.9%
FPG (mg/dL)		
Baseline	172	174
End of trial	106	113
Adjusted mean change from baseline	-71.1	-63.5
Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	59 U	62 U

*ODA: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region,

sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study E, there were 12.3% of subjects in the TRESIBA® and 12.7% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study F: TRESIBA® Administered at the Same Time Each Day in Insulin Naïve Adult Patients as an Add-on to One or More of the Following Oral Agents: Metformin, Sulfonylurea, Glinides or Alpha-Glucosidase Inhibitors

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in Asia in 435 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® once-daily in the evening or insulin glargine U-100 once-daily according to the approved labeling. Pre-trial oral antidiabetes agents were continued as background therapy except for DPP-4 inhibitors or thiazolidinediones in both treatment arms.

The mean age of the trial population was 58.6 years and mean duration of diabetes was 11.6 years. 53.6% were male. All patients were Asian. 10.9% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 25.0 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.11% with a 95% confidence interval of [-0.03%; 0.24%] and met the pre-specified non-inferiority margin (0.4%). See Table 11.

Table 11: Results at Week 26 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® + OAD(s)*	Insulin glargine U-100 + OAD(s)*
N	289	146
HbA_{1c} (%)		
Baseline	8.4	8.5
End of trial	7.2	7.1
Adjusted mean change from baseline**	-1.42	-1.52
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100	0.11 [-0.03; 0.24]	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	48.6%
FPG (mg/dL)		
Baseline	152	156
End of trial	100	102
Adjusted mean change from baseline	-54.6	-53.0
Daily insulin dose		
Baseline mean (starting dose)	9 U	9 U
Mean dose after 26 weeks	19 U	24 U

*ODA: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study F, there were 10% of subjects in the TRESIBA® and 6.8% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study G: TRESIBA® Administered at the Same Time Each Day or Any Time Each Day as an Add-on to One and up to Three of the Following Oral Agents: Metformin, Sulfonylurea or Glinides or Pioglitazone in Adult Patients

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 687 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone, oral antidiabetic agents (OADs) alone or both basal insulin and OAD. Patients were randomized to TRESIBA® injected once-daily at the same time each day (with the main evening meal), to TRESIBA® injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Up to three of the following oral antidiabetes agents (metformin, sulfonylureas, glinides or thiazolidinediones) were administered as background therapy in both treatment arms.

The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6 years. 53.9% were male. 66.7% were White, 2.5% Black or African American. 10.6% were Hispanic. 5.8% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 29.6 kg/m².

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA® at alternating times and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.12%; 0.20%]. This comparison met the pre-specified non-inferiority margin (0.4%). See Table 12.

Table 12: Results at Week 26 in a Trial Comparing TRESIBA® at Same and Alternating Times to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA® at the same time each day ± OAD(s)*	TRESIBA® at alternating times ± OAD(s)*	Insulin glargine U-100 ± OAD(s)*
N	228	229	230
HbA_{1c} (%)			
Baseline	8.4	8.5	8.4
End of trial	7.3	7.2	7.1
Adjusted mean change from baseline**	-1.03	-1.17	-1.21
Estimated treatment difference [95%CI] TRESIBA® alternating - Insulin glargine U-100		0.04 [-0.12;0.20]	
Estimated treatment difference TRESIBA® alternating – TRESIBA® same		-0.13	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	38.9%	43.9%
FPG (mg/dL)			
Baseline	158	162	163
End of trial	105	105	112
Adjusted mean change from baseline	-54.2	-55.0	-47.5
Daily insulin dose			
Baseline mean	21 U	19 U	19 U
Mean dose after 26 weeks	45 U	46 U	44 U

*OAD: oral antidiabetic agent

The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.In Study G, there were 11.4% subjects for TRESIBA® (both same time and alternating times) and 11.7% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.Study H: TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients**

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial in 992 patients with type 2 diabetes mellitus inadequately controlled on premix insulin, bolus insulin alone, basal insulin alone, oral antidiabetic agents (OADs) alone or any combination thereof. Patients were randomized to TRESIBA® once-daily with the main evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms. Up to two of the following oral antidiabetes agents (metformin or pioglitazone) were used as background therapy in both treatment arms.

The mean age of the trial population was 58.9 years and mean duration of diabetes was 13.5 years. 54.2% were male. 82.9% were White, 9.5% Black or African American. 12.0% were Hispanic. 12.4% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 32.2 kg/m².

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.08% with a 95% confidence interval of [-0.05%; 0.21%] and met the pre-specified non-inferiority margin (0.4%). See Table 13.

Table 13: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes and OADs*

	TRESIBA® + Insulin aspart ± OAD(s)*	Insulin glargine U-100 + Insulin aspart ± OAD(s)*
N	744	248
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline**	-1.10	-1.18
Estimated treatment difference [95%CI] TRESIBA® - Insulin glargine U-100		0.08 [-0.05;0.21]
Proportion Achieving HbA_{1c} < 7% at Trial End	49.5%	50.0%
FPG (mg/dL)		
Baseline	166	166
End of trial	122	127
Adjusted mean change from baseline	-40.6	-35.3
Daily basal insulin dose		
Baseline mean	42 U	41 U
Mean dose after 52 weeks	74 U	67 U
Daily bolus insulin dose		
Baseline mean	33 U	33 U
Mean dose after 52 weeks	70 U	73 U

*OAD: oral antidiabetic agent

The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.In Study H, there were 16.1% of subjects in the TRESIBA® and 14.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.Study I: TRESIBA® Administered at Any Time Each Day as an Add-on to One or Two of the Following Oral Agents: Metformin, Sulfonylurea, or Pioglitazone in Adult Patients**

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agent (OADs) at baseline. Patients were randomized to TRESIBA® once-daily at any time of day or sitagliptin once-daily according to the approved labeling. One or two of the following oral antidiabetes agents (metformin, sulfonylurea or pioglitazone) were also administered in both treatment arms.

The mean age of the trial population was 55.7 years and mean duration of diabetes was 7.7 years. 58.6% were male. 61.3% were White, 7.6% Black or African American. 21.0% were Hispanic. 6% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 30.4 kg/m².

At the end of 26 weeks, TRESIBA® provided greater reduction in mean HbA_{1c} compared to sitagliptin ($p < 0.001$). See Table 14.

Table 14: Results at Week 26 in a Trial Comparing TRESIBA® to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus on OADs*

	TRESIBA® + OAD(s)*	Sitagliptin + OAD(s)*
N	225	222
HbA_{1c} (%)		
Baseline	8.8	9.0
End of trial	7.2	7.7
Adjusted mean change from baseline**	-1.52	-1.09
Estimated treatment difference [95%CI] TRESIBA® - Sitagliptin		-0.43 [-0.61;-0.24] [†]
Proportion Achieving HbA_{1c} < 7% at Trial End	40.9%	27.9%
FPG (mg/dL)		
Baseline	170	179
End of trial	112	154
Adjusted mean change from baseline	-61.4	-22.3
Daily insulin dose		
Baseline mean	10 U	N/A
Mean dose after 26 weeks	43 U	N/A

*OAD: oral antidiabetic agent

The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.In Study I, there were 20.9% of subjects in the TRESIBA® and 22.5% Sitagliptin arms for whom data was missing at the time of the HbA_{1c} measurement.† $p < 0.001$; 1-sided p-value evaluated at 2.5% level for superiority16 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).

Table 15: Presentations of TRESIBA®

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

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.

Unopened 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]). Discard after expiration date.

Open (In-Use) FlexTouch® disposable prefilled pen:

The in-use TRESIBA® FlexTouch® pen should be refrigerated (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 16: Storage Conditions for TRESIBA® FlexTouch®

	Not in-use (unopened)	In-use (opened)	
	Refrigerated (36°F to 46°F [2°C to 8°C])	Room Temperature (below 86°F [30°C])	Refrigerated (36°F to 46°F [2°C to 8°C])
3 mL TRESIBA® U-100 FlexTouch®	Until expiration date	56 days (8 weeks)	56 days (8 weeks)
3 mL TRESIBA® U-200 FlexTouch®	Until expiration date	56 days (8 weeks)	56 days (8 weeks)

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.In Study H, there were 16.1% of subjects in the TRESIBA® and 14.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

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

Date of Issue: 12/2016

Version: 4

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PATENT Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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USA16TSM05264 January 2017



<p>Patient Information TRESIBA® (tre-SI-bah) (insulin degludec injection)</p> <p>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.</p> <p>What is TRESIBA®?</p> <ul style="list-style-type: none"> • 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. <p>Who should not take TRESIBA®?</p> <p>Do not take TRESIBA® if you:</p> <ul style="list-style-type: none"> • are having an episode of low blood sugar (hypoglycemia). • have an allergy to TRESIBA® or any of the ingredients in TRESIBA®. <p>Before taking TRESIBA®, tell your healthcare provider about all your medical conditions including, if you are:</p> <ul style="list-style-type: none"> • pregnant, planning to become pregnant, or are breastfeeding. • taking new prescription or over-the-counter medicines, vitamins, or herbal supplements. <p>Before you start taking TRESIBA®, talk to your healthcare provider about low blood sugar and how to manage it.</p> <p>How should I take TRESIBA®?</p> <ul style="list-style-type: none"> • 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®: <ul style="list-style-type: none"> ◦ Take your dose as soon as you remember then continue with your regular dosing schedule. ◦ Make sure there are at least 8 hours between your doses. • If children miss a dose of TRESIBA®: <ul style="list-style-type: none"> ◦ 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. <p>What should I avoid while taking TRESIBA®?</p> <p>While taking TRESIBA® do not:</p> <ul style="list-style-type: none"> • 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. <p>What are the possible side effects of TRESIBA®?</p> <p>TRESIBA® may cause serious side effects that can lead to death, including:</p> <ul style="list-style-type: none"> • Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include: <table border="0" style="width: 100%;"> <tr> <td style="width: 33%;"><input type="radio"/> dizziness or light-headedness</td> <td style="width: 33%;"><input type="radio"/> blurred vision</td> <td style="width: 33%;"><input type="radio"/> anxiety, irritability, or mood changes</td> </tr> <tr> <td><input type="radio"/> sweating</td> <td><input type="radio"/> slurred speech</td> <td><input type="radio"/> hunger</td> </tr> <tr> <td><input type="radio"/> confusion</td> <td><input type="radio"/> shakiness</td> <td><input type="radio"/> headache</td> </tr> <tr> <td><input type="radio"/> fast heartbeat</td> <td></td> <td></td> </tr> </table> • 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. 	<input type="radio"/> dizziness or light-headedness	<input type="radio"/> blurred vision	<input type="radio"/> anxiety, irritability, or mood changes	<input type="radio"/> sweating	<input type="radio"/> slurred speech	<input type="radio"/> hunger	<input type="radio"/> confusion	<input type="radio"/> shakiness	<input type="radio"/> headache	<input type="radio"/> fast heartbeat			<p>Your insulin dose may need to change because of:</p> <ul style="list-style-type: none"> • change in level of physical activity or exercise • weight gain or loss • increased stress • illness • change in diet <p>Common side effects of TRESIBA® may include:</p> <ul style="list-style-type: none"> • serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain. <p>Get emergency medical help if you have:</p> <ul style="list-style-type: none"> • trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion. <p>These are not all the possible side effects of TRESIBA®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.</p> <p>General information about the safe and effective use of TRESIBA®.</p> <p>Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRESIBA® that is written for health professionals. Do not use TRESIBA® for a condition for which it was not prescribed. Do not give TRESIBA® to other people, even if they have the same symptoms that you have. It may harm them.</p> <p>What are the ingredients in TRESIBA®?</p> <p>Active Ingredient: insulin degludec</p> <p>Inactive Ingredients: zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.</p> <p>Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark</p> <p>For more information, go to www.novonordisk-us.com or call 1-800-727-6500.</p>
<input type="radio"/> dizziness or light-headedness	<input type="radio"/> blurred vision	<input type="radio"/> anxiety, irritability, or mood changes											
<input type="radio"/> sweating	<input type="radio"/> slurred speech	<input type="radio"/> hunger											
<input type="radio"/> confusion	<input type="radio"/> shakiness	<input type="radio"/> headache											
<input type="radio"/> fast heartbeat													
This Patient Information has been approved by the U.S. Food and Drug Administration	Revised: 12/2016												

Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 200 units/mL (insulin degludec injection)

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

• TRESIBA® FlexTouch® Pen 200 units/mL ("Pen") is a pre-filled disposable pen containing 600 units of TRESIBA® (insulin degludec injection) 200 units/mL insulin. You can inject from 2 to 160 units in a single injection. The units can be increased by 2 units at a time.

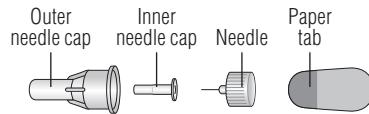
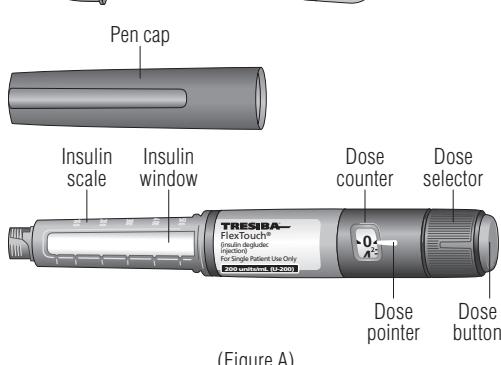
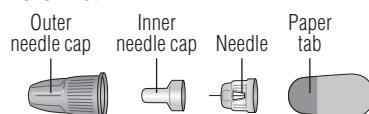
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your TRESIBA® injection:

- TRESIBA® FlexTouch® Pen
- a new NovoFine® or NovoTwist® needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See "After your injection" at the end of these instructions.

Preparing your TRESIBA® FlexTouch® Pen:

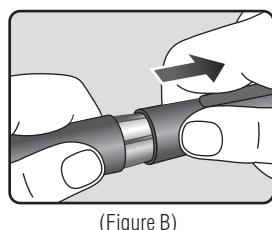
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the TRESIBA® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- TRESIBA® should look clear and colorless. Do not use TRESIBA® if it is cloudy or colored.
- Do not use TRESIBA® past the expiration date printed on the label or 56 days after you start using the Pen.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.

NovoFine®**NovoTwist®**

(Figure A)

Step 1:

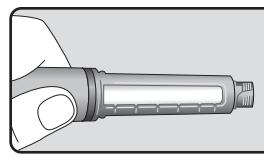
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

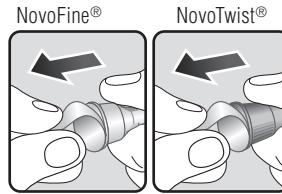
- Check the liquid in the Pen (See Figure C). TRESIBA® should look clear and colorless. Do not use it if it looks cloudy or colored.



(Figure C)

Step 3:

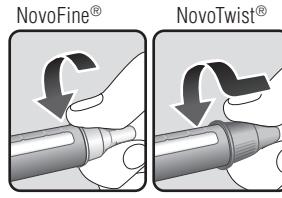
- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

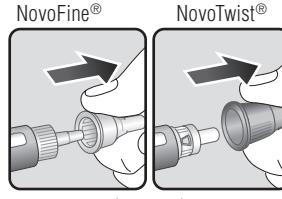
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

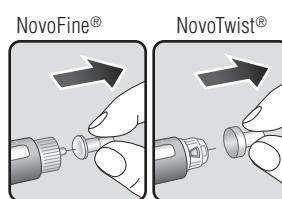
- Pull off the outer needle cap. Do not throw it away (See Figure F).



(Figure F)

Step 6:

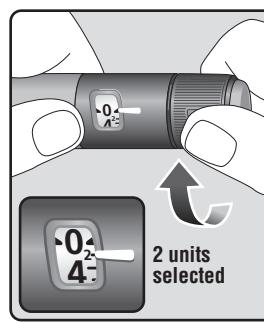
- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA® FlexTouch® Pen:**Step 7:**

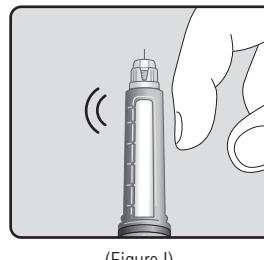
- Turn the dose selector to select 2 units (See Figure H).



(Figure H)

Step 8:

- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



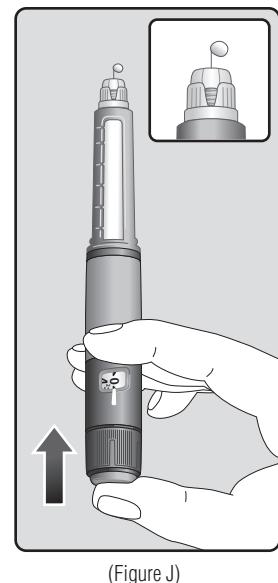
(Figure I)

Step 9:

- Hold the Pen with the needle pointing up. Press and hold the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.

- A drop of insulin should be seen at the needle tip (See Figure J).

- If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
- If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

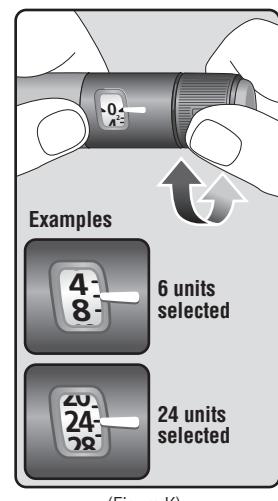
Selecting your dose:**Step 10:**

- TRESIBA® FlexTouch® Pen 200 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. Do not perform any dose conversion.

Check to make sure the dose selector is set at 0.

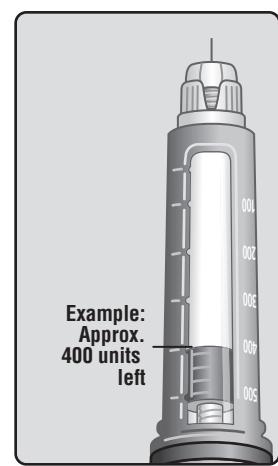
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).

- 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.



(Figure K)

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



(Figure L)

To see how much insulin is left in your TRESIBA® FlexTouch® Pen:

- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 160, there are at least 160 units left in your Pen.

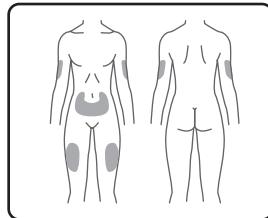
- If the dose counter shows less than 160, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your TRESIBA® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA® can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

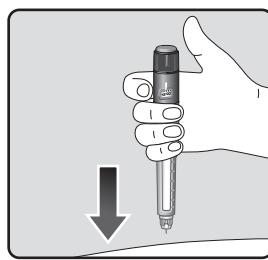
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

Step 12:

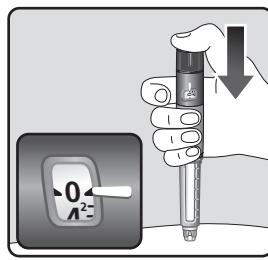
- Insert the needle into your skin (See Figure N).
 - Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.



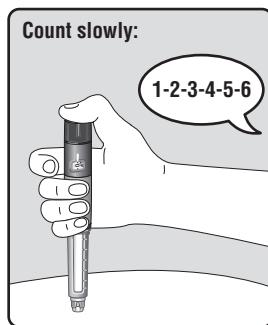
(Figure N)

Step 13:

- Press and hold down the dose button until the dose counter shows "0" (See Figure O).
 - The "0" must line up with the dose pointer. You may then hear or feel a click.
- Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6 (See Figure P).
 - When the dose counter returns to "0", you will not get your full dose until 6 seconds later.
 - If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
 - If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.



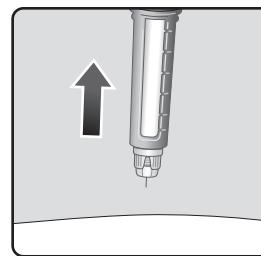
(Figure O)



(Figure P)

Step 14:

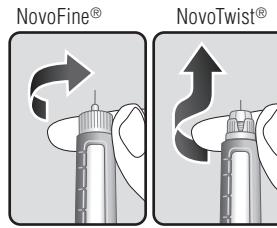
- Pull the needle out of your skin (See Figure Q).
 - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

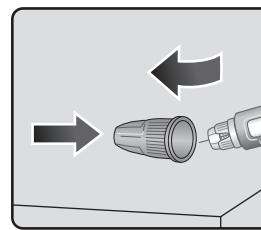
Step 15:

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



(Figure R)

- If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
 - Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.



(Figure S)

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:

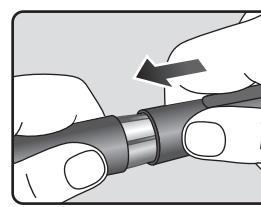
- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, 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.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used TRESIBA® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

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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USA16TSM05264 January 2017



Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 100 units/mL (insulin degludec injection)

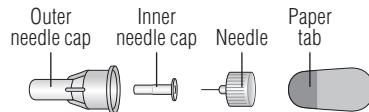
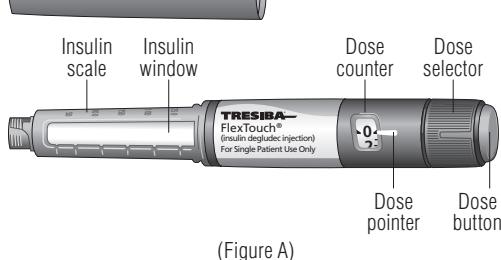
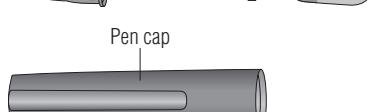
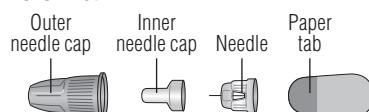
- **Do not share your TRESIBA® FlexTouch® Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **TRESIBA® FlexTouch® Pen 100 units/mL ("Pen") is a pre-filled disposable pen containing 300 units of TRESIBA® (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.**
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

Supplies you will need to give your TRESIBA® injection:

- TRESIBA® FlexTouch® Pen
 - a new NovoFine® or NovoTwist® needle
 - alcohol swab
 - a sharps container for throwing away used Pens and needles.
- See "After your injection" at the end of these instructions.**

Preparing your TRESIBA® FlexTouch® Pen:

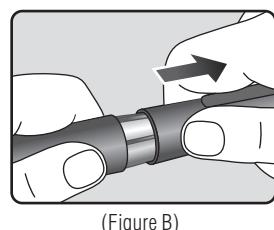
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the TRESIBA® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- TRESIBA® should look clear and colorless. **Do not** use TRESIBA® if it is cloudy or colored.
- **Do not** use TRESIBA® past the expiration date printed on the label or 56 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

NovoFine®**NovoTwist®**

(Figure A)

Step 1:

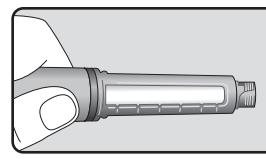
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

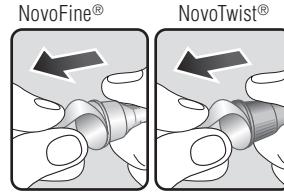
- **Check the liquid in the Pen** (See Figure C). TRESIBA® should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

Step 3:

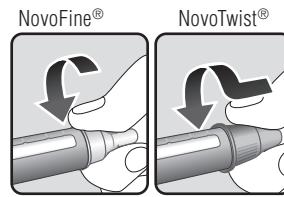
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

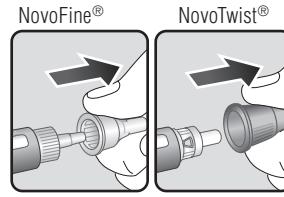
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

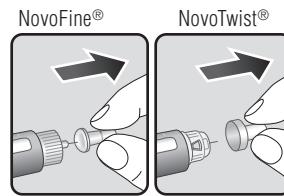
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

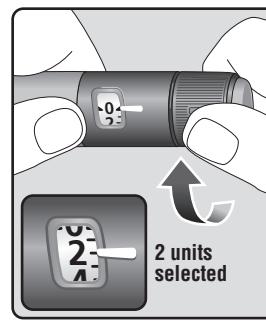
- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA® FlexTouch® Pen:**Step 7:**

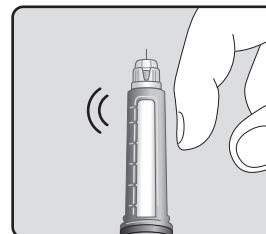
- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



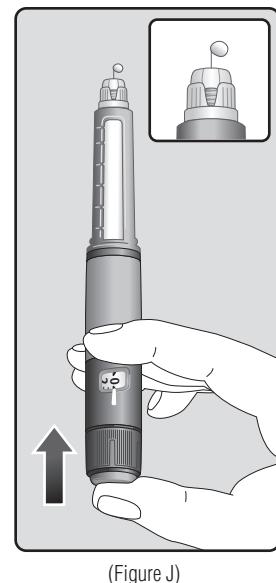
(Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.

- A drop of insulin should be seen at the needle tip (See Figure J).

- If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
- If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

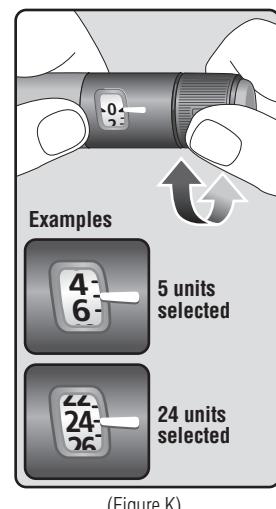
Selecting your dose:**Step 10:**

- TRESIBA® FlexTouch® Pen 100 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. **Do not perform any dose conversion.**

Check to make sure the dose selector is set at 0.

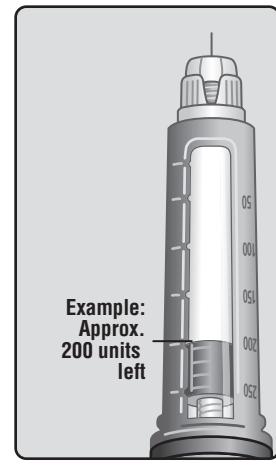
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).

- If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
- The **even** numbers are printed on the dial.
- The **odd** numbers are shown as lines.



(Figure K)

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



(Figure L)

- **To see how much insulin is left in your TRESIBA® FlexTouch® Pen:**

- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.

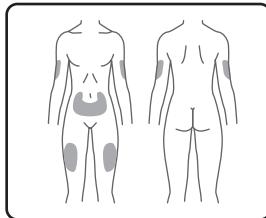
- If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your TRESIBA® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA® can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.

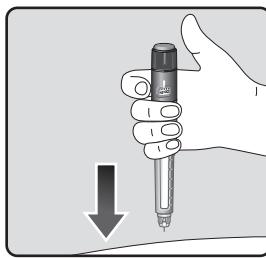


(Figure M)

Step 12:

- Insert the needle into your skin (See Figure N).

- Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

- Press and hold down the dose button until the dose counter shows "0" (See Figure O).

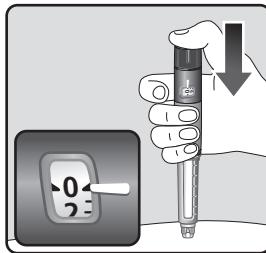
- The "0" must line up with the dose pointer. You may then hear or feel a click.

- Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6 (See Figure P).

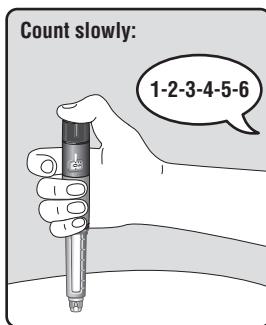
- When the dose counter returns to "0", you will not get your full dose until 6 seconds later.

- If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.

- If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.



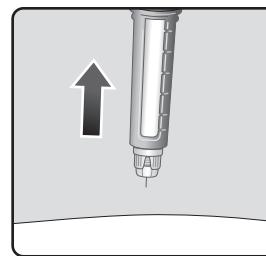
(Figure O)



(Figure P)

Step 14:

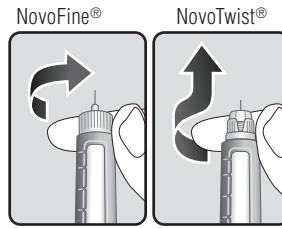
- Pull the needle out of your skin (See Figure Q).
 - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

Step 15:

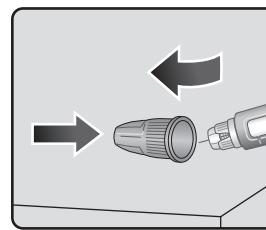
- Carefully remove the needle from the Pen and throw it away (See Figure R).
 - Do not recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

- Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.



(Figure S)

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:

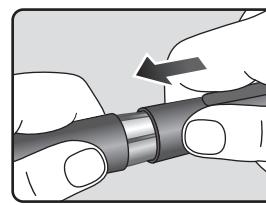
- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, 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.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used TRESIBA® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

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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