Questions?
Call 1-877-246-8910 to talk to a Certified Diabetes Educator.
Personal Progress Tracker
Fill in your blood sugar numbers.

Checking your blood sugar and tracking your numbers is an important part of your diabetes care plan. Your health care provider may have recommended testing your fasting plasma glucose (FPG). FPG tests measure your blood sugar after you haven’t eaten for 8 to 12 hours (or overnight). Most people check their FPG in the morning before they eat breakfast. Keep track of your FPG by filling in the information below every day.

Your numbers may change from day to day based on varying factors such as what you eat and how physically active you are. If you look at these numbers over time, you may start to see patterns in your blood sugar readings.

Here’s how to use your Blood Sugar Diary

1. Write the date.
2. Fill in your daily blood sugar numbers as your health care provider advises.
3. Mark how you feel today.

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Daily blood sugar numbers in the chart are for example only. You and your health care provider have established what your personal goals should be.

Please see additional Important Safety Information throughout. Please see Prescribing Information following page 7.
Fill in your blood sugar numbers and mark down how you are feeling. **Share this tracker with your health care provider to review your progress.** Your health care provider can use this information to make changes to your care plan to help you reach your goals.

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Eating healthy is an important part of your diabetes treatment plan. Find healthy, easy-to-prepare recipes on Cornerstones4Care.com.

Fill in your blood sugar numbers and mark down how you are feeling. Share this tracker with your health care provider to review your progress. Your health care provider can use this information to make changes to your care plan to help you reach your goals.

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Fill in your blood sugar numbers and mark down how you are feeling. **Share this tracker with your health care provider to review your progress.** Your health care provider can use this information to make changes to your care plan to help you reach your goals.

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Regular activity is a healthy habit to help you stay on track. Find tips for staying active at [Cornerstones4Care.com](http://Cornerstones4Care.com).
What is Tresiba®?

- Prescription Tresiba® is a long-acting insulin used to control high blood sugar in adults with diabetes
- Tresiba® is not for people with diabetic ketoacidosis
- Tresiba® is available in 2 concentrations: 200 units/mL and 100 units/mL
- It is not known if Tresiba® is safe and effective in children under 18 years of age

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
- 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
- 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 7.
You’ve used this tracker for your first 9 weeks. That’s great! Now keep it going.

Go to StartingTresiba.com and download your free Blood Sugar Tracker. You can use it to continue tracking your progress.
Severe, life-threatening, generalized allergy, including anaphylaxis, may occur. Discontinue TRESIBA® and treat if indicated (5.4).

Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TRESIBA® and treat if indicated (5.4).

Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.5).

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: 09/2015
TRESIBA® (insulin degludec injection)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRESIBA® is indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use

TRESIBA® is not recommended for the treatment of diabetic ketoacidosis.

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

- Inject TRESIBA® subcutaneously once-daily at any time of 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 (5.4)].
- 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.
- DO NOT perform dose conversion when using the TRESIBA® U-100 or U-200 FlexTouch® pens.

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

Type 1 and Type 2 Diabetes Mellitus:
Start TRESIBA® at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

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 Doseage 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)].

5.4 Hypoglycemia Due to Medication Errors

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)].

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 who have been treated with a fluid retaining medication should be monitored closely 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® was evaluated in nine treat to target trials of 6-12 months duration, conducted in subjects with type 1 diabetes or type 2 diabetes [see Clinical Studies (14)].

The data in Table 1 reflect the exposure of 1102 patients with type 1 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 54 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 HbA₁c at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 7% and 3% 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 patients with type 2 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 36 weeks. The mean age was 58 years and 3% were older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African American and 13% were Hispanic. The mean BMI was 30 kg/m². The mean duration of diabetes was 11 years and the mean HbA₁c at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 14%, 10%, 6% and 0.6% of participants respectively. At baseline, the mean eGFR was 83 mL/min/1.73 m² and 9% had an eGFR less than 60 mL/min/1.73 m².

Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA® treated subjects during clinical trials in patients with type 1 diabetes mellitus and 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.

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

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<tr>
<th>Adverse Reaction</th>
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<tr>
<td>Nasopharyngitis</td>
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<td>Upper respiratory tract infection</td>
<td>11.9 %</td>
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<tr>
<td>Headache</td>
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<td>Sinusitis</td>
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<td>Gastroenteritis</td>
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Table 2: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Patients with Type 2 Diabetes Mellitus

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<th>Adverse Reaction</th>
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<td>Nasopharyngitis</td>
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<tr>
<td>Headache</td>
<td>8.8 %</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<tr>
<td>Diarrhea</td>
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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 percent of participants randomized to TRESIBA® who experienced at least one episode of hypoglycemia in adult clinical trials [see Clinical Studies (14)] of patients with type 1 and type 2 diabetes respectively are shown in Table 3 and 4. No clinically important differences in risk of hypoglycemia between TRESIBA® and comparators was observed in clinical trials.

Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or 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).

Percent of Type 1 Diabetes Patients Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia® on TRESIBA® in Adult Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>TRESIBA® (N=472)</th>
<th>TRESIBA® (N=301)</th>
<th>TRESIBA® at the same time each day (N=165)</th>
<th>TRESIBA® at alternating times (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients</td>
<td>12.3 %</td>
<td>10.6 %</td>
<td>12.7 %</td>
<td>10.4 %</td>
</tr>
</tbody>
</table>

Novo Nordisk hypoglycemia

Percent of patients                  | 95.6 %           | 93.0 %           | 99.4 %                                   | 93.9 %                                |

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

Severe hypoglycemia

Percent of patients                  | 0.3 %            | 0 %              | 0.9 %                                    | 0.4 %                                  |

Novo Nordisk hypoglycemia

Percent of patients                  | 46.5 %           | 28.5 %           | 50 %                                     | 43.8 %                                  |

Subjects treated with TRESIBA® gained an average of 3.0 kg.

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 lipoatrophy (thinning 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 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 underestimated due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hypoglycemia or hyperglycemia.

The incidence of anti-insulin degludec antibodies has not been established.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with TRESIBA®.

Table 5: Clinically Significant Drug Interactions with TRESIBA®

<table>
<thead>
<tr>
<th>Drugs That May Increase the Risk of Hypoglycemia</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, dipeptidyl peptidase IV inhibitors, glucagon, luteinizing hormones, progestogens (e.g., in oral contraceptives), protease inhibitors, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.</td>
<td></td>
</tr>
<tr>
<td>Intervention: Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Drugs That May Blunt Signs and Symptoms of Hypoglycemia</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, clonidine, guanethidine, and reserpine.</td>
<td></td>
</tr>
<tr>
<td>Intervention: Increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
<td></td>
</tr>
</tbody>
</table>
5 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C

There are no well-controlled clinical studies of the use of insulin degludec in pregnant women. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Because animal reproduction studies are not always predictive of human response, insulin degludec should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

Subcutaneous reproduction and teratology studies have been performed with insulin degludec and human insulin (NPH) as a comparator in rats and rabbits. In these studies, insulin was given to female rats before mating throughout pregnancy until weaning, and to rabbits during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin as both caused pre-and post-implantation losses and visceral/skeletal abnormalities in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to maternal hypoglycemia.

8.2 Nursing Mothers

It is unknown whether insulin degludec is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when insulin degludec is administered to a nursing mother. Women with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

In rats, insulin degludec was secreted in milk and the concentration in milk was lower than in plasma.

8.4 Pediatric Use
The safety and efficacy of TRESIBA® in children and adolescents under the age of 18 have not been established.

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 dosage, 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 0 (0%) 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.

8.7 Hepatic Impairment

No 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.

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 glucose or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrences 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 [see Clinical Studies (14)].

Human Insulin

Structure of Human Insulin

\[
\text{Human Insulin} = \text{His} - \text{Gly} - \text{Cys} - \text{γ-Asn} - \text{Val} - \text{TRESIBA® (insulin degludec injection)}
\]

\[
\text{Cys} - \text{γ-Asn} - \text{Val} - \text{Pro}
\]

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.

8.8 Pregnancy

No clinically relevant difference in the pharmacokinetics of TRESIBA® was observed in the euglycemic 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.

8.9 Lactation

In rats, insulin degludec was secreted in milk and the concentration in milk was lower than in plasma.

8.10 Reproduction

In subgroup analyses comparing subjects older than 65 years to younger subjects.

8.11 Use in Specific Populations

8 USE IN SPECIFIC POPULATIONS

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Figure 1: Structural Formula of TRESIBA®
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 0.033 L/kg (2.1 L/h in 70 kg individual) after single subcutaneous dose of 0.4 U/kg.

### Specific Populations

As with other insulin preparations, TRESIBA® should always be titrated according to individual requirements.

- **Geriatrics**: Pharmacokinetic and pharmacodynamic response of TRESIBA® 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 U/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. 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. 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 Latin origin (n=18), White subjects of Hispanic or Latin origin (n=22) and White subjects not of Hispanic or Latin origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

- **Pregnancy**: The effect on the pharmacokinetics and pharmacodynamics of TRESIBA® has not been studied. [See Use in Specific Populations (8.1)].

### 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 U/kg/day), Sprague-Dawley rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 U/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 U/kg/day. Human insulin was dosed at 6.7 U/kg/day. Subjects requiring diastolic were classified as having end-stage renal disease (ESRD). Total (AUC(t-D;0,210h),so) 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/Fing,so) in subjects with ESRD [see Use in Specific Populations (8.6)].

#### 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. The efficacy of TRESIBA® administered once-daily either at the same time each day or at any time each day in 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.

#### 14.1 Type 1 Diabetes – Adult

**TRESIBA® Administered at the Same Time each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes**

**Study A**

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial in 629 patients with type 1 diabetes mellitus (Study A). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 58.5% were male, 93% were White, 1.9% Black or African American. 5.1% were Hispanic. 8.6% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 26.3 kg/m². At week 52, the difference in HbA1c reduction from baseline between TRESIBA® and insulin glargine U-100 was -0.01% with a 95% confidence interval of [-0.14%, 0.11%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study A.

**Study B**

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 455 patients with type 1 diabetes mellitus (Study B). Patients were randomized to TRESIBA® or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed twice-daily. 67.1% used insulin detemir once-daily at end of trial. 32.9% used insulin detemir twice daily at end of trial. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 13.9 years. 51.9% were male. 44.6% were White, 0.4% Black or African American. 4.4% were Hispanic. 4.4% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 29.2 kg/m². At week 26, the difference in HbA1c reduction from baseline between TRESIBA® and insulin detemir was -0.09% with a 95% confidence interval of [-0.23%, 0.05%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study B.

**TABLE 6: Results at Week 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 Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at Mealtimes**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>TRESIBA® + insulin aspart</th>
<th>Insulin glargine U-100 + insulin aspart</th>
<th>TRESIBA® + insulin aspart</th>
<th>Insulin detemir + insulin aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>472</td>
<td>157</td>
<td>302</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>165</td>
<td>174</td>
<td>178</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28 U</td>
<td>26 U</td>
<td>22 U</td>
<td>22 U</td>
<td></td>
</tr>
<tr>
<td>Mean dose at end of study</td>
<td>29 U²</td>
<td>31 U²</td>
<td>25 U²</td>
<td>29 U²</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29 U</td>
<td>29 U</td>
<td>28 U</td>
<td>31 U</td>
<td></td>
</tr>
<tr>
<td>Mean dose at end of study</td>
<td>32 U²</td>
<td>35 U²</td>
<td>36 U²</td>
<td>41 U²</td>
<td></td>
</tr>
</tbody>
</table>

1. At Week 52
2. At Week 26

**FGP (mg/dL):**

- Baseline mean: 28 U², 26 U², 22 U², 22 U²
- Mean dose at end of study: 29 U², 31 U², 25 U², 29 U²
- Baseline mean: 29 U², 29 U², 28 U², 31 U²
- Mean dose at end of study: 32 U², 35 U², 36 U², 41 U²

*HbA1c (%)**

- 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:
  - TRESIBA®: -0.36, -0.34, -0.71, -0.61
  - Insulin glargine U-100:
    - 0.01 [-0.14, 0.11]
    - 0.04 [-0.23, 0.05]

**Proportion Achieving HbA1c <7% at Trial End**

- 39.8%, 42.7%, 41.1%, 37.3%

**Daily basal insulin dose**

- Baseline mean: 28 U, 26 U, 22 U, 22 U
- Mean dose at end of study: 29 U², 31 U², 25 U², 29 U²
- Baseline mean: 29 U, 29 U, 28 U, 31 U
- Mean dose at end of study: 32 U², 35 U², 36 U², 41 U²

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

In Study A, there were 14.8% of subjects in the TRESIBA® and insulin glargine U-100 and 11.5% insulin glargine arms for whom data was missing at the time of the HbA1c 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 HbA1c 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**

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 both 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\textsubscript{c} reduction from baseline between TRESIBA\textsuperscript{®} 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\textsuperscript{®} Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin glargine U-100 in Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at mealtimes

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

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

14.2 Type 2 Diabetes – Adult

Study D: TRESIBA\textsuperscript{®} Administered at the Same Time Each day as an Add-on to Metformin with or without a DPP-4 inhibitor in Insulin Naïve Patients

The efficacy of TRESIBA\textsuperscript{®} was evaluated in a 26-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\textsuperscript{®} 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.

At week 26, the difference in HbA\textsubscript{c} reduction from baseline between TRESIBA\textsuperscript{®} 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 9.

Table 9: Results at Week 26 in a Trial Comparing TRESIBA\textsuperscript{®} U-200 to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus on OAD(s)*

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA\textsuperscript{®} U-200 + Met ± DPP-4</th>
<th>Insulin glargine U-100 + Met ± DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>228</td>
<td>229</td>
</tr>
<tr>
<td>HbA\textsubscript{c} (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
<td>8.2</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.8</td>
<td>-1.22</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>TRESIBA\textsuperscript{®} - Insulin glargine U-100</td>
<td>0.04 [-0.11;0.19]</td>
</tr>
<tr>
<td>Proportion Achieving HbA\textsubscript{c} &lt; 7% at Trial End</td>
<td>52.2%</td>
<td>55.9%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>172</td>
<td>174</td>
</tr>
<tr>
<td>End of trial</td>
<td>106</td>
<td>113</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-71.1</td>
<td>-63.5</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>10 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>59 U</td>
<td>62 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent
**The change from baseline to end of treatment visit in HbA\textsubscript{c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA\textsubscript{c} as covariates. In Study E, there were 10% of subjects in the TRESIBA\textsuperscript{®} and 6.8% insulin glargine arms for whom data was missing at the time of the HbA\textsubscript{c} measurement.

Study E: TRESIBA\textsuperscript{®} 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 Patients

The efficacy of TRESIBA\textsuperscript{®} 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\textsuperscript{®} 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/1.73m\textsupersquare{3}. The mean BMI was approximately 32.4 kg/m\textsupersquare{2}.

At week 26, the difference in HbA\textsubscript{c} reduction from baseline between TRESIBA\textsuperscript{®} 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 9.

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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA\textsuperscript{®} U-200 + Met ± DPP-4</th>
<th>Insulin glargine U-100 + Met ± DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>280</td>
<td>146</td>
</tr>
<tr>
<td>HbA\textsubscript{c} (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.4</td>
<td>8.5</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.42</td>
<td>-1.52</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>TRESIBA\textsuperscript{®} - Insulin glargine U-100</td>
<td>0.11 [-0.03 ; 0.24]</td>
</tr>
<tr>
<td>Proportion Achieving HbA\textsubscript{c} &lt; 7% at Trial End</td>
<td>40.8%</td>
<td>48.6%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>152</td>
<td>156</td>
</tr>
<tr>
<td>End of trial</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-54.6</td>
<td>-53.0</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (starting dose)</td>
<td>9 U</td>
<td>9 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>19 U</td>
<td>24 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent
**The change from baseline to end of treatment visit in HbA\textsubscript{c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA\textsubscript{c} as covariates. In Study F, there were 10% of subjects in the TRESIBA\textsuperscript{®} and 6.8% insulin glargine arms for whom data was missing at the time of the HbA\textsubscript{c} measurement.
The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multici
ter 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 labelling. The any time each day TRESIBA® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Up to three of the following oral antidiabetic agents (metformin, sulfonylureas, glinides or thiazolidinediones) were administered as background therapy in both treatment arms. The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6 years. 59.9% 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 HbA1c 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 11.

### Table 11: Results at Week 26 in a Trial Comparing TRESIBA® at Same and alternating times to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus on OAD(s)*

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® at the same time each day ± OAD(s)**</th>
<th>TRESIBA® at alternating times ± OAD(s)**</th>
<th>Insulin glargine U-100 ± OAD(s)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>228</td>
<td>229</td>
<td>230</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.3</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>End of trial</td>
<td>-1.03</td>
<td>-1.17</td>
<td>-1.21</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>0.04 [-0.12;0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference (95%CI) TRESIBA® alternating - Insulin glargine U-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference TRESIBA® alternating - TRESIBA® same</td>
<td>-0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>40.8%</td>
<td>38.9%</td>
<td>43.9%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>158</td>
<td>162</td>
<td>163</td>
</tr>
<tr>
<td>Baseline</td>
<td>105</td>
<td>105</td>
<td>112</td>
</tr>
<tr>
<td>End of trial</td>
<td>-54.2</td>
<td>-50.0</td>
<td>-47.5</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td>21 U</td>
<td>19 U</td>
<td>19 U</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>45 U</td>
<td>46 U</td>
<td>44 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily bolus insulin dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates. In Study I, 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 HbA1c measurement. The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multici
ter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agent (OADs) at baseline. Patients were randomized to TRESIBA® once-daily at any time of day or sitagliptin once-daily according to the approved labeling. One or two of the following oral antidiabetic agents (metformin, sulfonylurea or pioglitazone) were also administered in both treatment arms. The mean age of the trial population was 55.7 years and mean duration of diabetes was 77 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 32.2 kg/m². At the end of 26 weeks, TRESIBA® provided greater reduction in mean HbA1c compared to sitagliptin (p < 0.001). See Table 13.

### Table 12: Results at Week 52 in a Trial Comparing TRESIBA® to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus receiving Insulin aspart at mealtimes and OADs**

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + Insulin aspart ± OAD(s)**</th>
<th>Insulin glargine U-100 + Insulin aspart ± OAD(s)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>744</td>
<td>248</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>End of trial</td>
<td>-1.10</td>
<td>-1.18</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-0.04 [-0.05;0.21]</td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference (95%CI) TRESIBA® - Insulin glargine U-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>49.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>166</td>
<td>166</td>
</tr>
<tr>
<td>Baseline</td>
<td>122</td>
<td>127</td>
</tr>
<tr>
<td>Mean dose after 52 weeks</td>
<td>74 U</td>
<td>67 U</td>
</tr>
<tr>
<td>Daily bolus insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>33 U</td>
<td>33 U</td>
</tr>
<tr>
<td>Mean dose after 52 weeks</td>
<td>70 U</td>
<td>73 U</td>
</tr>
</tbody>
</table>

**OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates. In Study 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 HbA1c measurement.
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRESIBA® is available as a clear and colorless solution in the following package sizes (see Table 14).

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

16.2 Recommended Storage

Unused TRESIBA® should be stored between 36°F to 46°F (2°C and 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.

Unopen FlexTouch® disposable prefilled pen:
Not in-use (unopened) TRESIBA® disposable prefilled pen should be stored in a refrigerator (36°F - 46°F [2°C - 8°C]). Discard after expiration date.

Open (In-Use) FlexTouch® disposable prefilled pen:
The in-use TRESIBA® FlexTouch® pen should NOT be refrigerated but should 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 kept at room temperature.

The storage conditions are summarized in Table 15:

<table>
<thead>
<tr>
<th>TRESIBA®</th>
<th>Not-in-use (unopened)</th>
<th>Not-in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FlexTouch®</td>
<td>Refrigerated (36°F - 46°F [2°C - 8°C])</td>
<td>Room Temperature (below 86°F [30°C])</td>
<td>Room Temperature (below 86°F [30°C])</td>
</tr>
<tr>
<td>3 mL</td>
<td>Until expiration date</td>
<td>56 days (8 weeks)</td>
<td>56 days (8 weeks)</td>
</tr>
<tr>
<td>3 mL</td>
<td>Until expiration date</td>
<td>56 days (8 weeks)</td>
<td>56 days (8 weeks)</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

See 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 bloodborne 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 may predispose to hyper- or hypoglycemia.

Advise patients that changes in insulin regimen should be made under close medical supervision [see Warnings and Precautions (5.2)].

Medication errors

Inform patients to always check the insulin label before each injection [see Warnings and Precautions (5.4)]. TRESIBA® FlexTouch® pen is available in concentrations of 100 units/mL or 200 units/mL. Inform patients that the dose counter of TRESIBA® FlexTouch® pen shows the number of units of TRESIBA® to be injected. NO dose re-calculation is required [see Dosage and Administration (2.2)].

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

- If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would not have received any insulin – even though the dose counter has moved from the original dose that was set.
- If the patient did have a blocked or damaged needle, instruct them to change the needle as described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting with a new needle and the Section Preparing your TRESIBA® FlexTouch® Pen. Make sure the patient selects the full dose needed.

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

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

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

Administration

TRESIBA® must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that TRESIBA® must NOT be diluted or mixed with any other insulin or solution [see Dosage and Administration (2.1)].

Management of Hypoglycemia and Handling of Special Situations

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

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

Women of Reproductive Potential

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

Rx Only

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Version: 1

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TRESIBA® is covered by US Patent No. 7,615,532 and other patents pending. FlexTouch® is covered by US Patent Nos. 6,899,699, 6,786,786, 8,672,898, 8,684,969, 8,920,383, D724,721, D734,450 and other patents pending.

Manufactured by:
Novo Nordisk A/S
DK-2860 Bagsvaerd, Denmark

For information about TRESIBA® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
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www.novonordisk-us.com

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Do not share your TRESIBA® FlexTouch® insulin delivery device with other people, even if the needle has changed. You may give other people a serious infection, or get a serious infection from them.

What is TRESIBA®?
- TRESIBA® is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.
- TRESIBA® is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- 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.
- It is not known if TRESIBA® is safe and effective in children under 18 years of age.

Who should not take TRESIBA®?
Do not take TRESIBA® if you:
- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to TRESIBA® or any of the ingredients in TRESIBA®.

Before taking TRESIBA®, tell your healthcare provider about all your medical conditions including, if you are:
- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking TRESIBA®, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take TRESIBA®?
- Read the Instructions for Use that come with your TRESIBA®.
- Take TRESIBA® exactly as your healthcare provider tells you to.
- Do not do any conversion of your dose. The dose counter always shows the selected dose in units. Both the 100 units/mL and 200 units/mL TRESIBA® FlexTouch® pens are made to deliver your insulin dose in units.
- Know the type and strength of insulin you take. Do not change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss or are delayed in taking your dose of TRESIBA®:
  - Take your dose as soon as you remember, but do not delay your next dose.
  - Make sure there are at least 8 hours between your doses.
- Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.
- Never inject TRESIBA® into a vein or muscle.
- Never use a syringe to remove TRESIBA® from the FlexTouch® pen.

What should I avoid while taking TRESIBA®?
While taking TRESIBA® do not:
- Drive or operate heavy machinery, until you know how TRESIBA® affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of TRESIBA®?
TRESIBA® may cause serious side effects that can lead to death, including:
- Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - sweating
  - confusion
  - fast heartbeat
  - Low potassium in your blood (hypokalemia).
  - Heart failure. Taking certain diabetes pills called thiazolidinediones or “TZDs” with TRESIBA® may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with TRESIBA®. Your healthcare provider should monitor you closely while you are taking TZDs with TRESIBA®. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, tiredness, swelling of your ankles or feet and sudden weight gain. Treatment with TZDs and TRESIBA® may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:
- change in level of physical activity or exercise
- weight gain or loss
- Common side effects of TRESIBA® may include:
  - serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.
- These are not all the possible side effects of TRESIBA®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRESIBA®.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRESIBA® that is written for health professionals. Do not use TRESIBA® for a condition for which it was not prescribed. Do not give TRESIBA® to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in TRESIBA®?
Active Ingredient: insulin degludec
Inactive Ingredients: zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.
Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 09/2015
Instructions for Use
TRESIBA® (tre-SI-bah) FlexTouch® Pen 200 units/mL (insulin degludec injection)

- Do not share your TRESIBA® FlexTouch® Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.
- TRESIBA® FlexTouch® Pen 200 units/mL ("Pen") is a prefilled disposable pen containing 600 units of TRESIBA® (insulin degludec injection) 200 units/mL insulin. You can inject from 2 to 160 units in a single injection. The units can be increased by 2 units at a time.
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your TRESIBA® injection:
- TRESIBA® FlexTouch® Pen
- a new NovoFine® or NovoTwist® needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See “After your injection” at the end of these instructions.

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

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

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

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

Step 2:
- Check the liquid in the Pen (See Figure C). TRESIBA® should look clear and colorless. Do not use it if it looks cloudy or colored.

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

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

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

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

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

Step 8:
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

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.

Step 10: Selecting your dose:
- TRESIBA® FlexTouch® Pen 200 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. Do not perform any dose conversion.
- Check to make sure the dose selector is set at 0.
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - Each line on the dial is an even number.

Examples
- 4 units selected
- 24 units selected

To see how much insulin is left in your TRESIBA® FlexTouch® Pen:
- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 160, there are at least 160 units left in your Pen.
  - If the dose counter shows less than 160, the number shown in the dose counter is the number of units left in your Pen.
Giving your injection:

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

Step 11:

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

Step 12:

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

Step 13:

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

Step 14:

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

Step 15:

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

Step 16:

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

After your injection:

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

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 out of the refrigerator below 86°F.
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days, 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.
Instructions for Use
TRESIBA® (tre-SI-bah) FlexTouch® Pen 100 units/mL (insulin degludec injection)

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

• TRESIBA® FlexTouch® Pen 100 units/mL ("Pen") is a prefilled disposable pen containing 300 units of TRESIBA® (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.

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

Supplies you will need to give your TRESIBA® injection:
• TRESIBA® FlexTouch® Pen
• a new NovoFine® or NovoTwist® needle
• alcohol swab
• a sharps container for throwing away used Pens and needles. See “After your injection” at the end of these instructions.

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

NovoFine®
Outer needle cap
Inner needle cap
Needle
Paper tab

NovoTwist®
Outer needle cap
Inner needle cap
Needle
Paper tab
Pen cap
Insulin scale
Insulin window
Dose counter
Dose selector
Dose pointer
Dose button

Step 1:
• Pull Pen cap straight off (See Figure B).

Step 2:
• Check the liquid in the Pen (See Figure C). TRESIBA® should look clear and colorless. Do not use it if it looks cloudy or colored.

Step 3:
• Select a new needle.
  • Pull off the paper tab from the outer needle cap (See Figure D).
  • Push the capped needle straight onto the Pen and twist the needle on until it is light (See Figure E).

Step 4:
• Pull off the outer needle cap. Do not throw it away (See Figure F).

Step 5:
• Pull off the outer needle cap and throw it away (See Figure G).

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

Step 7:
• Turn the dose selector to select 2 units (See Figure I).

Step 8:
• Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

Step 9:
• Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows “0”. The “0” must line up with the dose pointer.
• A drop of insulin should be seen at the needle tip (See Figure J).
  o If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  o If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.

Selecting your dose:

Step 10:
TRESIBA® FlexTouch® Pen 100 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. Do not perform any dose conversion.

Check to make sure the dose selector is set at 0.
• Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
  o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  o The even numbers are printed on the dial.
  o The odd numbers are shown as lines.

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

• To see how much insulin is left in your TRESIBA® FlexTouch® Pen:
  o 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.
  o 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 (hips), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

Step 11:

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

Step 12:

- Insert the needle into your skin (See Figure N).
  - Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.
- Press and hold down the dose button until the dose counter shows “0” (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.
- Pull the needle out of your skin (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

Step 13:

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

Step 14:

- 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.
- 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.
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Before use:

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- 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 out of the refrigerator below 86°F.
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days, 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.