Getting Started on Tresiba® FlexTouch®

Tresiba® U-200 FlexTouch® is the only basal insulin pen delivering up to 160 units in a single injection

**Tresiba® U-200 FlexTouch®**
- Works with NovoFine® or NovoTwist® needles
- Prefilled with 600 units of Tresiba®
- Select the dose in 2-unit increments
- Dark green label
- Maximum of 160 units per dose

**Tresiba® U-100 FlexTouch®**
- Light green label
- Maximum of 80 units per dose
- Select the dose in 1-unit increments
- Prefilled with 300 units of Tresiba®
- Works with NovoFine® or NovoTwist® needles

Both Tresiba® U-200 and U-100 FlexTouch® pens last up to 8 weeks unrefrigerated, compared with 4 weeks for Lantus® SoloSTAR® and 6 weeks for Toujeo® SoloSTAR®.

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**Tresiba® FlexTouch® use**
- Never share insulin pens with anyone, even if you attach a new pen needle
- Use a new pen needle for every injection
- Remove pen needle after every injection and discard it into a puncture-resistant container
- Do not store Tresiba® FlexTouch® with the needle attached
- If the Tresiba® FlexTouch® pen isn’t working properly, perform a function check according to the Patient Instructions For Use

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**Detailed guidance is only a call, click, or visit away**

- **Novo Nordisk Customer Care**
  Call 1-800-727-6500 to speak with a customer care representative about Tresiba® FlexTouch®

- **Physician & Pharmacist**
  Contact your doctor or pharmacist to learn more about Tresiba® FlexTouch®

- **Tresiba® Website**
  Go to Tresiba.com for instructions and a training video on using Tresiba® FlexTouch®

- **Cornerstones4Care®**
  Support and diabetes management tools built around you. Enroll today to get FREE, personalized diabetes support at Cornerstones4Care.com

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**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

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**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®

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Please see additional Important Safety Information on next page.
Please see Prescribing Information following page 2.
A Guide to Using Your Tresiba® FlexTouch®

Prepare your pen

- Check your insulin type
  - Read the label to check that you have the right insulin. Make sure the insulin is clear and colorless.

Attach a new needle
- Pull off the paper tab. Push and twist the needle on until it is tight. Pull off both needle caps.

Prime your pen
- Turn the dose selector to select 2 units. Press and hold the dose button. Make sure a drop appears.

Give your injection

- Select your dose
  - Turn the dose selector to select the number of units you need to inject.
  - U-200: Each line on the dial is an even number.
  - U-100: Even numbers are printed on the dial; odd numbers are shown as lines.

- Count slowly:
  - 1-2-3-4-5-

- Give your injection
  - Insert the needle in the thigh, upper arm, or abdomen. Press and hold the dose button. After the dose counter reaches 0, slowly count to 6.\(^*\)

- Remove the needle
  - Carefully remove the needle and place it in a sharps container. Replace the pen cap.

Important Safety Information (cont’d)

Who should not take Tresiba®? (cont’d)

Before taking Tresiba®, tell your health care provider about all your medical conditions, including if you are:

- pregnant, planning to become pregnant, or are breastfeeding
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements

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

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.

For a free FlexTouch® training session, please call 1-877-246-8910 to talk to a FlexTouch® Pen Specialist 9 AM to 6 PM (ET) Monday–Friday

\(^*\)Please note that if the needle is removed before the 6-second count is completed after the dose counter returns to “0,” then underdosing may occur by as much as 20%, resulting in the need for increasing the frequency of checking blood sugar and possible additional insulin administration.

Please see Prescribing Information beginning next page.
TRESIBA®
insulin degludec injection

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

——— INDICATIONS AND USAGE ———
TRESIBA® is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1).

Limitations of Use:
Not recommended for treating diabetic ketoacidosis.

——— 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 inject dilute or mix with any other insulin or solution (2.1).
• Administer subcutaneously once daily at any time of day (2.2).
• Do not dilute or mix with any other insulin or solution (2.1).
• Rotate injection sites to reduce the risk of lipodystrophy (2.1).
• 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).

——— 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: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*
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2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
2.2 General Dosing Instructions
2.3 Starting Dose in Insulin Naïve Patients
2.4 Starting Dose in Patients Already on Insulin Therapy
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Never Share a TRESIBA® FlexTouch® Pen Between Patients
5.2 Hypoglycemia or Hypoglycemia with Changes in Insulin Regimen
5.3 Hypoglycemia
5.4 Hypoglycemia Due to Medication Errors
5.5 Hypersensitivity and Allergic Reactions
5.6 Hypokalemia
5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist
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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 (5.2)].
• 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, 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.

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 not be treated with a PPAR-gamma agonist at baseline, if at baseline, the mean eGFR was less than 60 mL/min/1.73 m 2.

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 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 HbA1c at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 6% and 0.6% of participants respectively. At baseline, the mean eGFR 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...
Table 1: Adverse Reactions Occurring in ≥5% of TRESIBA®-Treated Patients with Type 1 Diabetes Mellitus

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

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

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

Hypoglycemia

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

The 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 in adult clinical trials [see Clinical Studies (14)] were observed in clinical trials.

Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucose, or other resuscitative actions. 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 Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Example</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>insulin aspart 52 weeks</td>
<td>TRESIBA® (N=472)</td>
</tr>
<tr>
<td>B</td>
<td>insulin aspart 26 weeks</td>
<td>TRESIBA® (N=301)</td>
</tr>
<tr>
<td>C</td>
<td>insulin aspart 26 weeks</td>
<td>TRESIBA® at the same time each day (N=165)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRESIBA® at alternating times (N=164)</td>
</tr>
</tbody>
</table>

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%

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Example</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>OAD* insulin naive 52 weeks</td>
<td>TRESIBA® (N=766)</td>
</tr>
<tr>
<td>E</td>
<td>OAD* insulin naive 26 weeks</td>
<td>TRESIBA® (N=228)</td>
</tr>
<tr>
<td>F</td>
<td>OAD* insulin naive 26 weeks</td>
<td>TRESIBA® (N=284)</td>
</tr>
<tr>
<td>G</td>
<td>OAD* insulin naive 26 weeks</td>
<td>TRESIBA® (N=226)</td>
</tr>
<tr>
<td>H</td>
<td>T2DM ± OAD* insulin aspart 26 weeks</td>
<td>TRESIBA® (N=575)</td>
</tr>
<tr>
<td>I</td>
<td>T2DM ± OAD* insulin aspart 26 weeks</td>
<td>TRESIBA® (N=226)</td>
</tr>
</tbody>
</table>

Severe hypoglycemia

Percent of patients 0.3% 0.0% 0.9% 0.4% 4.5% 0.4%

Novo Nordisk hypoglycemia §

Percent of patients 46.5% 28.5% 50% 43.8% 50.9% 80.9% 42.5%

Table 5: Clinically Significant Drug Interactions with TRESIBA®

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents</td>
<td>ACE inhibitors, angiotensin II receptor blocking agents, dipeptidyl peptidase IV inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
<td>Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
</tr>
<tr>
<td>Antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, proton pump inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
<td>Dose increases and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.</td>
<td></td>
</tr>
<tr>
<td>Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.</td>
<td>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 6: Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA® is co-administered with these drugs.
TRESIBA® (insulin degludec injection) is a sterile, aqueous, clear, and colorless solution that contains insulin degludec: 100 units/mL (U-100) or 200 units/mL (U-200).

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

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

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

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

The primary activity of insulin, including TRESIBA®, is regulation of glucose metabolism. Insulin and its analog has a 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 protein synthesis. TRESIBA® forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The prolonged 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 U/kg dose of TRESIBA® (steady state) in patients with type 1 diabetes mellitus](image)

The mean maximum glucose lowering effect (GIRmax) of a 0.4 U/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 AUC0-inf)(2,3).

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 U/kg to 0.8 U/kg.

The total glucose-lowering effect of 0.4 U/kg of TRESIBA® U-100 and 0.4 U/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 were comparable.

12.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 U/kg of TRESIBA®, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (tmax).

After the first dose of TRESIBA®, median onset of appearance was around one hour.

Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 U/kg to 0.8 U/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 U/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 of TRESIBA® 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.
TRESIBA® (insulin degludec injection)

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 at the time of 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 29.9 kg/m². At week 26, the difference in HbA1c reduction from baseline between TRESIBA® and insulin detemir was -0.05% 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 A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRESIBA® + Insulin aspart</td>
<td>Insulin glargine U-100 + Insulin aspart</td>
</tr>
<tr>
<td>N</td>
<td>472</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.7</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.3</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.36</td>
</tr>
<tr>
<td>Estimated treatment difference (95%CI) TRESIBA® - Insulin glargine U-100</td>
<td>-0.01 [-0.14;0.11]</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>39.8%</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 6.5% at Trial End</td>
<td>14.1%</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>165</td>
</tr>
<tr>
<td>End of trial</td>
<td>141</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-27.6</td>
</tr>
<tr>
<td>Daily basal insulin dose</td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>31 U</td>
</tr>
<tr>
<td>Mean dose at end of study</td>
<td>29 U</td>
</tr>
<tr>
<td>Daily bolus insulin dose</td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>28 U</td>
</tr>
<tr>
<td>Mean dose at end of study</td>
<td>29 U</td>
</tr>
</tbody>
</table>

*At Week 52

*At Week 26

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 A, there were 14.8% of subjects in the TRESIBA® and 11.5% insulin-glargin-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.

Study A

Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe).

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. There were no statistically significant differences between the racial and ethnic groups investigated.

Pregnancy

The effect on the pregnancy of the pharmacokinetics and pharmacodynamics of TRESIBA® has not been studied.

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 5.3, 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. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were observed in male and female 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 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75 U/kg/day, based on U/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. 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. Patients treated with TRESIBA® achieved levels of glycemic control similar to those achieved with LANTUS (insulin glargine 100 U/mL) and LEVEMIR® (insulin detemir) and achieved statistically significant improvements compared to sitagliptin.
**TRESIBA® (insulin degludec injection)**

At week 26, the difference in HbA1c 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 Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at mealtimes

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® at the same time each day + Insulin aspart</th>
<th>TRESIBA® 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>HbA1c (%)</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® alternating - Insulin glargine U-100</td>
<td>0.17 [0.04; 0.30]</td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &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>
</tbody>
</table>

### 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 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 C, there were 15.8% and 15.9% of subjects in the TRESIBA® (same time and alternating times respectively) and 7.9% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 32.4 kg/m².

### 14.2 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 Patients**

The efficacy of TRESIBA® 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® 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 (82.5%) or in combination with a DPP-4 inhibitor (17.5%) 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 HbA1c 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 9.

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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® 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>HbA1c (%)</td>
<td>8.3</td>
<td>8.2</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>-1.18</td>
<td>-1.22</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>TRESIBA® - Insulin glargine U-100</td>
<td>0.04 [-0.11; 0.19]</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>52.2%</td>
<td>55.9%</td>
</tr>
</tbody>
</table>

### Daily bolus insulin dose

- Baseline mean: 10 U, 10 U
- Mean dose after 26 weeks: 59 U, 62 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in 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 F, there were 12.3% of subjects in the TRESIBA® and 12.7% Insulin glargine arms for whom data was missing at the time of the HbA1c measurement.

### 14.2.1 Type 2 Diabetes – Adult

**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 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 HbA1c 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 Patients with Type 2 Diabetes Mellitus on OAD(s)***

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® U-200 + OAD(s)</th>
<th>Insulin glargine U-100 + OAD(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>280</td>
<td>146</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>152</td>
<td>156</td>
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<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>Estimated treatment difference [95%CI]</td>
<td>TRESIBA® - Insulin glargine U-100</td>
<td>0.11 [-0.03; 0.24]</td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>40.8%</td>
<td>48.6%</td>
</tr>
</tbody>
</table>

### Daily bolus insulin dose

- Baseline mean (starting dose): 9 U, 9 U
- Mean dose after 26 weeks: 19 U, 24 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in 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 F, there were 12.3% of subjects in the TRESIBA® and 12.7% Insulin glargine arms for whom data was missing at the time of the HbA1c measurement.
### Study G: TRESIBA® Administered at the Same Time Each Day or Any Time Each Day as an Add-on to OADs

The efficacy of TRESIBA® was evaluated in a 26-week, randomized, open-label, multicenter trial in 667 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone, oral antidiabetic agents (OADs) alone, or both basal insulin and OADs. 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 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 HbA1c reduction from baseline between TRESIBA® 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® alternating times ± OAD(s)**</th>
<th>Insulin glargine U-100 ± OAD(s)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>8.4</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>7.3</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.03</td>
<td>-1.17</td>
<td>-1.21</td>
</tr>
<tr>
<td>Est. treatment difference [95% CI] TRESIBA® alternating - Insulin glargine U-100</td>
<td>0.04 [-0.12;0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21 U</td>
<td>19 U</td>
<td>19 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>45 U</td>
<td>46 U</td>
<td>44 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 G, there were 11.4% subjects for TRESIBA® (both same time and alternating times) and 11.7% Insulin glargine U-100 who had data missing at the time of the HbA1c measurement.

### Study H: TRESIBA® Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes

The efficacy of TRESIBA® was evaluated in a 52-week, randomized, open-label, multicenter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® once-daily at any time of day or sitagliptin once-daily at any time of day or sitagliptin once-daily according to the approved labelling. 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 58.7 years and mean duration of diabetes was 7.7 years. 58.6% were male. 61.3% were White, 7.6% Black or African American. 21.0% were Hispanic. 6% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 30.4 kg/m². At the end of 26 weeks, TRESIBA® provided greater reduction in mean HbA1c compared to sitagliptin (p < 0.001). See Table 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><strong>HbA1c (%)</strong></td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.10</td>
<td>-1.18</td>
</tr>
<tr>
<td>Estimated treatment difference [95% CI] TRESIBA® - Insulin glargine U-100</td>
<td>0.08 [-0.05;0.26]</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><strong>FGP (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>166</td>
<td>166</td>
</tr>
<tr>
<td>Mean dose after 52 weeks</td>
<td>122</td>
<td>127</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-40.6</td>
<td>-35.3</td>
</tr>
<tr>
<td>Daily bolus insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</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 16.1% of subjects in the TRESIBA® and 14.5% Insulin glargine U-100 who had data missing at the time of the HbA1c measurement.

### Table 13: Results at Week 26 in a Trial Comparing TRESIBA® to Sitagliptin in Patients with Type 2 Diabetes Mellitus on OADs*

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + OAD(s)**</th>
<th>Sitagliptin + OAD(s)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.52</td>
<td>-1.09</td>
</tr>
<tr>
<td>Estimated treatment difference [95% CI] TRESIBA® - Sitagliptin</td>
<td>-0.43 [-0.61; -0.24]</td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>40.9%</td>
<td>27.9%</td>
</tr>
<tr>
<td><strong>FGP (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>170</td>
<td>179</td>
</tr>
<tr>
<td>Mean dose after 52 weeks</td>
<td>112</td>
<td>154</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-61.4</td>
<td>-22.3</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10 U</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>43 U</td>
<td>N/A</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.

*p < 0.001; 1-sided p-value evaluated at 2.5% level for superiority.
Instruct Patients to never use a syringe to remove TRESIBA® from the FlexTouch® disposable prefilled pen. The risk of blocked needles increases the risk of under-dosing or overdosing. Instruct patients to not re-use needles. A new needle must be attached before each injection. Reuse of needles slightly increase the dialed insulin dose to achieve the patient's glycemic targets.

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>FlexTouch®</th>
<th>Not in-use (unopened)</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></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]) Do not refrigerate</td>
</tr>
<tr>
<td>U-100</td>
<td>Until expiration date</td>
<td>56 days (8 weeks)</td>
<td>56 days (8 weeks) Do not refrigerate</td>
</tr>
<tr>
<td>U-200</td>
<td>Until expiration date</td>
<td>56 days (8 weeks)</td>
<td>56 days (8 weeks) Do not refrigerate</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 reduce 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.

Rx Only

Date of Issue: 09/2015

Version: 1

Novo Nordisk®, TRESIBA®, FlexTouch®, LEVEMIR®, NOVOLOG®, NovoFine® and NovoTwist® are registered trademarks of Novo Nordisk A/S.

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-2880 Bagsvaerd, Denmark
For information about TRESIBA® contact: Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500
www.novonordisk-us.com
© 2015 Novo Nordisk
USA1STSMM06353 September 2015
TRESIBA® (insulin degludec injection)

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

What is TRESIBA®?

- TRESIBA® is a man-made insulin that is used to control high blood sugar in adults 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 then continue with your regular dosing schedule.
  - 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
- increased stress
- change in diet
- weight gain or loss
- illness

Common side effects of TRESIBA® may include:

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of TRESIBA®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRESIBA®.

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

What are the ingredients in TRESIBA®?

Active Ingredient: insulin degludec

Inactive Ingredients: zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

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

Revised: 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 sharps container for throwing away used Pens and needles.
• alcohol swab
• a new NovoFine® or NovoTwist® needle

• Do not share your TRESIBA® FlexTouch® Pen with another person. You may 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.

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.

Steps 1 to 7:
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).

Steps 8 to 10:
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).
  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 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).
  o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  o Each line on the dial is an even number.

• 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 160, there are at least 160 units left in your Pen.
  o 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.
  ○ 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 recap the needle. Recapping the needle can lead to needle stick injury.
• Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6 (See Figure P).
  ○ When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  ○ If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
  ○ If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.

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

Step 14:
• Pull the needle out of your skin (See Figure Q).
  ○ If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

Step 15:
• Carefully remove the needle from the Pen and throw it away (See Figure R).
  ○ Do not recap the needle. Recapping the needle can lead to needle stick injury.
  ○ If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
  ○ Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:
• Replace the Pen cap by pushing it straight on (See Figure T).

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

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 88°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).

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

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

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

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

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

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

Selecting your dose:
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The even numbers are printed on the dial.
  - The odd numbers are shown as lines.

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

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

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

**Step 14:** Pull the needle out of your skin (See Figure Q).
- If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

**Step 15:** Carefully remove the needle from the Pen and throw it away (See Figure R).
- Do not recap the needle. Recapping the needle can lead to needle stick injury.
- If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
- Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

**Step 16:** Replace the Pen cap by pushing it straight on (See Figure T).

After your injection:

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

**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.