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

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use TRESIBA® safely and effectively. See full prescribing information for TRESIBA®. TRESIBA® (insulin degludec injection), for subcutaneous use
Initial U.S. Approval: 2015

--- RECENT MAJOR CHANGES ---
Dosage and Administration (2.1) 11/2019
Warnings and Precautions (5.2) 11/2019

--- INDICATIONS AND USAGE ---
TRESIBA® is a long-acting human insulin analog indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus (1).

--- DOSAGE AND ADMINISTRATION ---
See Full Prescribing Information for important administration instructions (2.1).
Inject TRESIBA® subcutaneously into the thigh, upper arm, or abdomen (2.1).
Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis (2.1).
For pediatric patients requiring less than 5 units of TRESIBA® each day, use a TRESIBA® U-100 vial (2.1).
In adults, inject subcutaneously once daily at any time of day (2.2).
In pediatric patients inject subcutaneously once daily at the same time every day (2.2).
Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal (2.2).
The recommended days between dose increases are 3 to 4 days (2.2).
See Full Prescribing Information for recommended starting dose in insulin naive patients and patients already on insulin therapy (2.3, 2.4).

--- DOSAGE FORMS AND STRENGTHS ---
TRESIBA® injection is available in the following package sizes:
• 100 units/mL (U-100): 3 mL single-patient-use FlexTouch® (3).
• 200 units/mL (U-200): 3 mL single-patient-use FlexTouch® (3).
• 100 units/mL (U-100): 10 mL multiple-dose vial (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).
Hyperglycemia or hypoglycemia with changes in insulin regimen: Make changes to a patient’s insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased 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 (5.1).
Hypoglycemia unawareness (5.3, 5.4, 6.1).

--- ADVERSE REACTIONS ---
Adverse reactions commonly associated with TRESIBA® are:
• hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---
• Drugs that may increase the risk of hypoglycemia: antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fifies, fluoxetine, monamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7).
• Drugs that may decrease the blood glucose lowering effect: atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7).
• Drugs that may increase or decrease the blood glucose lowering effect: Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7).
• Drugs that may blunt the signs and symptoms of hypoglycemia: beta-blockers, clonidine, guanethidine, and reserpine (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 11/2019

--- CLINICAL STUDIES ---
14.1 Type 1 Diabetes – Adult
14.2 Type 1 Diabetes – Pediatric Patients 1 Year of Age and Older
14.3 Type 2 Diabetes – Adult
14.4 Safety Outcomes Trial

--- HOW SUPPLIED/STORAGE AND HANDLING ---
16.1 How Supplied
16.2 Recommended Storage

--- PATIENT COUNSELING INFORMATION ---
*Sections or subsections omitted from the full prescribing information are not listed.
TRESIBA® (insulin degludec injection)

FULL PRESCRIBING INFORMATION

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

Limitations of Use

• Not recommended for the treatment of diabetic ketoacidosis.

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.

2.2 General Dosing Instructions

• TRESIBA® is available in 2 concentrations (U-100 and U-200):
  - TRESIBA® U-100 concentration is available in 2 presentations, FlexTouch® pen and vial
  - Single-patient-use TRESIBA® U-100 FlexTouch® pen contains 300 units of TRESIBA® U-100.
  - It delivers doses in 1 unit increments and can deliver up to 80 units in a single injection.
  - TRESIBA® U-100 multiple-dose vial contains 1000 units of TRESIBA® U-100. Use vial only with a U-100 insulin syringe.
  - TRESIBA® U-200 concentration is available in a FlexTouch® pen
  - Single-patient-use TRESIBA® U-200 FlexTouch® pen contains 600 units of TRESIBA® U-200.
  - It delivers doses in 1 unit increments and can deliver up to 160 units in a single injection.

• DO NOT perform dose conversion when using the TRESIBA® U-100 or U-200 pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

• For adults, inject TRESIBA® subcutaneously once-daily at any time of day.
• In pediatric patients inject TRESIBA® subcutaneously once-daily at the same time every day.
• Individualize and titrate the dose of TRESIBA® based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal.

• The recommended days between dose increases are 3 to 4 days.

• Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [see Warnings and Precautions (5.3)].

• For adults, instruct patients who miss a dose of TRESIBA® to inject their daily dose during waking hours upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive TRESIBA® injections.
• For pediatric patients, instruct patients who miss a dose of TRESIBA® to contact their healthcare provider for guidance and to monitor blood glucose levels more frequently until the next scheduled TRESIBA® dose.

2.3 Starting Dose in Insulin Naïve Patients

Type 1 Diabetes Mellitus:

The recommended starting dose of TRESIBA® in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus:
The recommended starting dose of TRESIBA® in insulin naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients Already on Insulin Therapy

Adults with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA® at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA® at 60% of the total daily long or intermediate-acting insulin unit dose to minimize the risk of hypoglycemia [see Warnings and Precautions (5.2)].

3 DOSAGE FORMS AND STRENGTHS

Injection: TRESIBA® is available as a clear and colorless solution:

• 100 units/mL (U-100); 3 mL single-patient-use FlexTouch® disposable prefilled pen
• 100 units/mL (U-100); 10 mL multiple-dose vial
• 200 units/mL (U-200); 3 mL single-patient-use FlexTouch® disposable prefilled pen

4 CONTRAINDICATIONS

TRESIBA® is contraindicated:

• During episodes of hypoglycemia [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a TRESIBA® FlexTouch® Pen, Needle, or Syringe Between Patients

TRESIBA® FlexTouch® disposable prefilled pens should never be shared between patients, even if the needle is changed. Patients using TRESIBA® vials should never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.3)] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia [see Adverse Reactions (6.1, 6.3)].

Make any changes to a patient’s insulin regimen under close medical supervision with increased insulin. Instruct patients to closely monitor blood glucose and contact their healthcare provider if they experience symptoms of hypoglycemia or hyperglycemia.

5.3 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

When used in combination with a PPAR-gamma agonist, treatment with TRESIBA® may cause fluid retention and congestive heart failure. In patients with diabetic nephropathy or one of its excipients [see Warnings and Precautions (5.3)].

5.4 Hypoglycemia Due to Medication Errors

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

To avoid dosing errors and potential overdose, never use a syringe to remove TRESIBA® from the TRESIBA® FlexTouch® disposable insulin prefilled pen [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 with standard 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 (4.9)].

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 difficulty, cardiac arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin, including TRESIBA® and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be...
managed according to current standards of care and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia [see Warnings and Precautions (5.3)]
- Medication errors [see Warnings and Precautions (5.4)]
- Hypersensitivity and allergic reactions [see Warnings and Precautions (5.5)]
- Hypokalemia [see Warnings and Precautions (5.6)]

6.1 Clinical Trial Experience

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

The safety of TRESIBA® in subjects with type 1 diabetes or type 2 diabetes was evaluated in nine trials of 6-12 month duration in adults and in one trial of 12-month duration in pediatric patients 1 year of age and older with type 1 diabetes. The cardiovascular safety of TRESIBA® was evaluated in one double-blinded, event-driven trial of 2-year median duration in patients with type 2 diabetes at high risk of cardiovascular events [see Clinical Studies (14)]

The data in Table 1 reflect the exposure of 1102 adults with type 1 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 34 weeks in three open-label trials. The mean age was 43 years and 1% were older than 75 years. Fifty-seven percent were male, 81% were White, 2% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 26 kg/m². The mean duration of diabetes was 18 years and the mean HbA1c at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 7% and 0.5% respectively. The mean eGFR at baseline was 87 ml/min/1.73 m² and 7% of the patients had an eGFR less than 60 ml/min/1.73 m².

The data in Table 2 reflect the exposure of 2713 adults with type 2 diabetes to TRESIBA® with a mean exposure duration to TRESIBA® of 36 weeks in three open-label trials. The mean age was 58 years and 3% were older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African American and 13% were Hispanic. 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 8% respectively. At baseline, the mean eGFR was 83 ml/min/1.73 m² and 9% had an eGFR less than 60 ml/min/1.73 m². Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA® treated subjects during clinical trials in adult patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

174 pediatric patients 1 year of age and older with type 1 diabetes were exposed to TRESIBA® with a mean exposure duration to TRESIBA® of 48 weeks. The mean age was 10 years: 25% were ages 1-5 years, 40% were ages 6-11 years, and 35% were ages 12-17 years. 55.2% were male, 78.2% were White, 2.9% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 18.7 kg/m². The mean duration of diabetes was 3.9 years and the mean HbA1c at baseline was 8.2%. Common adverse reactions in TRESIBA® treated pediatric patients with type 1 diabetes mellitus were similar to the adverse reactions listed in Table 1.

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TRESIBA® (N=2713)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nauseopharyngism</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.

In the open-label adult clinical trials of patients with type 1 and type 2 diabetes, and in the open-label pediatric clinical trial of patients with type 1 diabetes, percentages of adult and pediatric patients with type 1 diabetes randomized to TRESIBA® who experienced at least one episode of hypoglycemia in clinical trials [see Clinical Studies (14)] and adults with type 2 diabetes are shown in Tables 3 and 4, respectively.

Severe hypoglycemia in the open-label trials with adult patients was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia in the pediatric trial was defined as an altered mental status where the child could not assist in his own care, was semicomaous or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).

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

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

<table>
<thead>
<tr>
<th>Study / Treatment</th>
<th>N</th>
<th>Severe hypoglycemia*</th>
<th>Novo Nordisk hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A Adults + insulin aspart 52 weeks</td>
<td>766</td>
<td>12.3%</td>
<td>93.0%</td>
</tr>
<tr>
<td>Study B Adults + insulin aspart 26 weeks</td>
<td>301</td>
<td>10.6%</td>
<td>99.4%</td>
</tr>
<tr>
<td>Study C Adults + insulin aspart 26 weeks</td>
<td>165</td>
<td>12.7%</td>
<td>93.9%</td>
</tr>
<tr>
<td>Study J Pediatrics + insulin aspart 52 weeks</td>
<td>174</td>
<td>10.4%</td>
<td>98.3%</td>
</tr>
</tbody>
</table>

*Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semicomaous or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).

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

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

<table>
<thead>
<tr>
<th>Study / Treatment</th>
<th>N</th>
<th>Severe hypoglycemia*</th>
<th>Novo Nordisk hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study D 1-2 OADs* insulin naïve 52 weeks</td>
<td>766</td>
<td>0.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Study E 1-2 OADs* insulin naïve 26 weeks</td>
<td>228</td>
<td>0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Study F 1-2 OADs* insulin naïve 26 weeks</td>
<td>284</td>
<td>0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Study G T2DM ± aspart 52 weeks</td>
<td>226</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Study H T2DM ± aspart 52 weeks (alternating time)</td>
<td>230</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Study I T2DM ± aspart 52 weeks (alternating time)</td>
<td>753</td>
<td>0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

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

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including TRESIBA® and may be life threatening [see Warnings and Precautions (5.3)]. Hypersensitivity (manifested with swelling of tongue and lips, diaphoresis, nausea, 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 lipo hypertrophy (excessive deposits of adipose tissue) and may affect insulin absorption [see Dosage and Administration (2.1)]. In the clinical program, lipodystrophy, lipo hypertrophy, 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®. Weight gain can occur with TRESIBA® treated patients with type 1 diabetes mellitus and 30% of patients with type 2 diabetes mellitus treated with TRESIBA®.

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 30% 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 a 52-week study of adult insulin-experienced type 1 diabetes patients, 68.9% of patients who received TRESIBA® were positive at baseline for anti-insulin degludec antibodies and 12.3% of the patients developed anti-insulin degludec antibodies at least once during the study. In a 52-week study of pediatric insulin-experienced type 1 diabetes patients, 84.1% of patients who received TRESIBA® were positive at baseline for anti-insulin degludec antibodies and 5.8% of patients developed anti-insulin degludec antibodies at least once during the study. In a 52-week study of adult insulin-naïve type 2 diabetes patients, 1.7% of patients who received TRESIBA® were positive at baseline for anti-insulin degludec antibodies and 6.2% of patients developed anti-insulin degludec antibodies at least once during the study. In these trials, between 96.7% and 99.7% of patients who were positive for anti-insulin degludec antibodies were also positive for anti-human insulin antibodies.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of TRESIBA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hyperglycemia has been reported with a sudden change to an unaffected injection site.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with TRESIBA®.

Table 5: Clinically Significant Drug Interactions with TRESIBA®

<table>
<thead>
<tr>
<th>Drugs That May Increase the Risk of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Intervention:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Blunt Signs and Symptoms of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with TRESIBA® or insulin degludec in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Rats and rabbits were exposed to insulin degludec in animal reproduction studies during organo-genesis. Pre- and post-implantation losses and visceral/skeletal abnormalities were observed in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

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

Data

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

8.3 Pediatric Use

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

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

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

8.4 Geriatric Use

In controlled clinical studies [see Clinical Studies (14)] of a total of 77 (%) 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 to the effects of TRESIBA® cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.5 Renal Impairment

In clinical studies [see Clinical Studies (14)] of a total of 75 (%) of the 1102 TRESIBA®-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m² and 1 (0.1%) had an eGFR less than 30 mL/min/1.73 m². A total of 250 (9%) of the 2713 TRESIBA®-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m² and no subjects had an eGFR less than 30 mL/min/1.73 m². In the safety outcomes trial (DEVOTE), a total of 1429 (37.4%) of the 3818 TRESIBA®-treated patients with type 2 diabetes were 65 years or older and 381 (10%) were 75 years or older. Differences in safety or effectiveness were not observed in these subgroup analyses.

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

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

11 DESCRIPTION

TRESIBA® (insulin degludec injection) is a long-acting basal human insulin analog for subcutaneous injection. Insulin degludec is produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification.
Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29Ne-hexadecanoyl-γ-Glu) des(B30) human insulin). Insulin degludec has a molecular formula of C212H328N132O102S12 and a molecular weight of 6103.97. It has the following structure:

Figure 1: Structural Formula of TRESIBA®

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

For the 100 units/mL solution, each mL contains 100 units (600 nmol) of insulin degludec and glycerol (19.6 mg), metacresol (1.72 mg), phenol (1.50 mg), zinc (52.7 mcg), and Water for Injection, USP.

For the 200 units/mL solution, each mL contains 200 units (1200 nmol) of insulin degludec and glycerol (19.6 mg), metacresol (1.72 mg), phenol (1.50 mg), zinc (71.9 mcg), and Water for Injection, USP.

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 action of insulin, including TRESIBA®, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteinolysis, and enhances protein synthesis. TRESIBA® forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of TRESIBA® is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

12.2 Pharmacodynamics

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

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

The mean maximum glucose lowering effect (GIRmax) of a 0.4 units/kg dose of TRESIBA® was 2.0 mg/dL, 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 AUCGIR,t.5). The total glucose-lowering effect of TRESIBA® over 24 hours measured in a euglycemic clamp study after 8 days of once-daily administration in patients with type 1 diabetes increases approximately in proportion to the dose for doses between 0.4 units/kg to 0.8 units/kg. The total glucose-lowering effect of 0.4 units/kg of TRESIBA® U-100 and 0.4 units/kg of TRESIBA® U-200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study after 8 days of once-daily injection was comparable.

12.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 units/kg of TRESIBA®, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (tmax). After the first dose of TRESIBA®, median onset of appearance was around one hour. Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 units/kg to 0.8 units/kg TRESIBA®. Total and maximum insulin degludec exposure at steady state are comparable between TRESIBA® U-100 and TRESIBA® U-200 when each is administered at the same units/kg dose. Insulin degludec concentration reached steady state levels after 3-4 days of TRESIBA® administration [see Dosage and Administration (2.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Genotoxicity testing of insulin degludec was not performed.

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

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

Adult patients treated with TRESIBA® achieved levels of glycemic control similar to those achieved with LANTUS® (insulin glargine 100 units/mL) and LEVEMIR® (insulin detemir) and achieved statistically significant improvements compared to sitagliptin.

14.1 Type 1 Diabetes – Adult

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

Study A

The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial in 629 patients with type 1 diabetes mellitus (Study A). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms. The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 58.5% were male. 93% were White, 1.9% Black or African American. 5.1% were Hispanic. 8.6% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 26.3 kg/m².

At week 52, the difference in 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 one-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 43 years and mean duration of diabetes was 18.9 years. 51.9% were male. 44.6% were White, 0.4% Black or African American, 4.4% Hispanic. 4.4% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 23.9 kg/m².

At week 26, the difference in HbA₁c reduction from baseline between TRESIBA® and insulin detemir was −0.09% with a 95% confidence interval of [−0.23%; 0.05%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study B.

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

<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>Study A</td>
<td>472</td>
<td>157</td>
<td>302</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.7</td>
<td>7.7</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean change from baseline*</td>
<td>−0.36</td>
<td>−0.34</td>
<td>−0.71</td>
<td>−0.61</td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference [95% CI]</td>
<td>−0.01 [−0.14; 0.11]</td>
<td>−0.09 [−0.23; 0.05]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA₁c &lt; 7% at Trial End</td>
<td>39.8%</td>
<td>42.7%</td>
<td>41.3%</td>
<td>37.3%</td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>165</td>
<td>174</td>
<td>178</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>148</td>
<td>149</td>
<td>137</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>−2.7</td>
<td>−2.5</td>
<td>4.3</td>
<td>−1.3</td>
<td></td>
</tr>
<tr>
<td>Daily basal insulin dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>28 U</td>
<td>28 U</td>
<td>22 U</td>
<td>22 U</td>
<td></td>
</tr>
<tr>
<td>Mean dose at end of study</td>
<td>29 U</td>
<td>31 U</td>
<td>25 U</td>
<td>29 U</td>
<td></td>
</tr>
<tr>
<td>Daily bolus insulin dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>22 U</td>
<td>23 U</td>
<td>23 U</td>
<td>31 U</td>
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<tr>
<td>Mean dose at end of study</td>
<td>32 U</td>
<td>35 U</td>
<td>36 U</td>
<td>41 U</td>
<td></td>
</tr>
</tbody>
</table>

At Week 26

At Week 26

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

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

In Study B, there were 8.3% 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 in Adult Patients

The efficacy of TRESIBA® was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to TRESIBA® injected once-daily at the same time each day (with the main evening meal), to TRESIBA® injected once-daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 57.8% were male. 96.7% were White, 1.8% Black or African American. 3.4% were Hispanic. 74.0% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 26.7 kg/m².

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 Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

<table>
<thead>
<tr>
<th>N</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>165</td>
<td>164</td>
<td>164</td>
<td></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>−0.01 [0.04, 0.30]</td>
<td></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>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 HbA₁c was analyzed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline BMI as covariates.

In Study C, there were 15.8% and 15.9% of subjects in the TRESIBA® (same time and alternating times respectively) and 7.9% insulin glargine arms for whom data was missing at the time of the HbA₁c measurement.

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

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

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

The mean age of the trial population was 10 years; 24% were ages 1-5 years; 39% were ages 6-11 years and 36% were ages 12-17 years. The mean duration of diabetes was 4 years. 55.4% were male. 44.6% were White, 0.4% Black or African American, 4.4% Hispanic. 4.4% of patients had eGFR < 60 mL/min/1.73m². The mean BMI was approximately 22 U (0.52 U/kg) and 29 U (0.52 U/kg). The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years.
The efficacy of TRESIBA® was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naive patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Metformin alone (82.5%) or in combination with a DPP-4 inhibitor (17.5%) was used as background therapy in both treatment arms. The mean age of the trial population was 59.1 years and mean duration of diabetes was 9.2 years. 61.9% were male. 88.4% were White, 7.1% Black or African American. 17.2% were Hispanic. 9.6% of patients had eGFR<60 mL/min/1.73m². The mean BMI was approximately 31.1 kg/m².

At week 52, the difference in HbA1c reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.09% with a 95% confidence interval of (-0.04%; 0.22%) and met the pre-specified non-inferiority margin (0.4%). See Table 9.

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

<table>
<thead>
<tr>
<th></th>
<th>TRESIBA® + OAD(s)*</th>
<th>Insulin glargine U-100 + OAD(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>773</td>
<td>257</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>End of trial</td>
<td>7.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Adjusted mean change from baseline**</td>
<td>-1.06</td>
<td>-1.15</td>
</tr>
<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>0.03 [-0.02; 0.04]</td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>51.7%</td>
<td>54.1%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>174</td>
<td>174</td>
</tr>
<tr>
<td>End of trial</td>
<td>106</td>
<td>115</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-60.2</td>
<td>-60.2</td>
</tr>
<tr>
<td>Daily insulin dose</td>
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<td></td>
</tr>
<tr>
<td>Baseline mean (starting dose)</td>
<td>10 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Mean dose after 52 weeks</td>
<td>56 U</td>
<td>58 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent
**The change from baseline to end of treatment visit in HbA1c was analyzed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates. In Study D, there were 20.6% of subjects in the TRESIBA® and 22.2% Insulin glargine arms for whom data was missing at the time of the HbA1c measurement.

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

The efficacy of TRESIBA® U-200 was evaluated in a 26-week randomized, open-label, multicenter trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA® U-200 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Both treatment arms were receiving metformin alone (84%) or in combination with a DPP-4 inhibitor (16%) as background therapy. The mean age of the trial population was 57.5 years and mean duration of diabetes was 8.2 years. 53.2% were male. 79.3% 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 Adult 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>
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<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>
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<td>Adjusted mean change from baseline**</td>
<td>-1.18</td>
<td>-1.22</td>
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<tr>
<td>Estimated treatment difference [95%CI]</td>
<td>0.04 [-0.11;0.19]</td>
<td></td>
</tr>
<tr>
<td>Proportion Achieving HbA1c &lt; 7% at Trial End</td>
<td>52.2%</td>
<td>55.9%</td>
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<td>FPG (mg/dL)</td>
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<td>Baseline</td>
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<td>Adjusted mean change from baseline</td>
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</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (starting dose)</td>
<td>10 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Mean dose after 26 weeks</td>
<td>59 U</td>
<td>62 U</td>
</tr>
</tbody>
</table>

*OAD: oral antidiabetic agent
**The change from baseline to end of treatment visit in HbA1c was analyzed 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 10% of subjects in the TRESIBA® and 6.8% Insulin glargine arms for whom data was missing at the time of the HbA1c measurement.

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

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

The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6 years. 53.9% were male. 67.1% 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 12.
Table 12: Results at Week 26 in a Trial Comparing TRESIBA® at Same and Alternating Times to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

<table>
<thead>
<tr>
<th>N</th>
<th>Baseline</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>
<th>Adjusted mean change from baseline</th>
<th>Estimated treatment difference 95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>228</td>
<td>8.4</td>
<td>6.5</td>
<td>8.4</td>
<td>-1.9</td>
<td>0.04 [-0.12;0.20]</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>229</td>
<td>7.3</td>
<td>7.2</td>
<td>7.1</td>
<td>-0.1</td>
<td>-0.13</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>230</td>
<td>8.4</td>
<td>6.8</td>
<td>8.4</td>
<td>-1.6</td>
<td>-1.21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Proportion Achieving HbA1c < 7% at Trial End

FPG (mg/dL)

Baseline 156 162 163
End of trial 105 105 112

Adjusted mean change from baseline

-54.2 -55.0 -47.5

Daily insulin dose

Baseline mean 21 U 19 U 19 U
Mean dose after 26 weeks 45 U 46 U 44 U

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

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

The mean age of the trial population was 58.9 years and mean duration of diabetes was 13.5 years. 54.2% were male. 95.9% were White or Black or African American. 12.0% were Hispanic. 12.4% of patients had eGFR <60 mL/min/1.73m². The mean BMI was approximately 32.2 kg/m².

At week 52, the difference in HbA1c reduction from baseline between TRESIBA® and insulin glargine U-100 was 0.08% with a 95% confidence interval of [-0.05; 0.21%] and met the pre-specified non-inferiority margin (0.4%). See Table 13.

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

<table>
<thead>
<tr>
<th>N</th>
<th>Baseline</th>
<th>TRESIBA® + insulin aspart ± OAD(s)*</th>
<th>Insulin glargine U-100 + insulin aspart ± OAD(s)*</th>
<th>Adjusted mean change from baseline</th>
<th>Estimated treatment difference 95%CI</th>
<th>Proportion Achieving HbA1c &lt; 7% at Trial End</th>
<th>FPG (mg/dL)</th>
<th>Daily Basal insulin dose</th>
<th>Daily bolus insulin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>744</td>
<td>8.3</td>
<td>6.5</td>
<td>8.4</td>
<td>-1.9</td>
<td>-0.08 [-0.05;0.21]</td>
<td>49.5%</td>
<td>168</td>
<td>122</td>
<td>42 U</td>
</tr>
<tr>
<td>248</td>
<td>7.1</td>
<td>7.2</td>
<td>7.1</td>
<td>-0.02</td>
<td>-1.18</td>
<td>50.0%</td>
<td>166</td>
<td>127</td>
<td>41 U</td>
</tr>
</tbody>
</table>

Proportion Achieving HbA1c < 7% at Trial End

FPG (mg/dL)

Baseline 162 166
End of trial 122 127

Adjusted mean change from baseline

-40.6 -35.3

Daily basal insulin dose

Baseline mean 42 U 41 U
Mean dose after 52 weeks 74 U 67 U

Daily bolus insulin dose

Baseline mean 33 U 33 U
Mean dose after 52 weeks 70 U 73 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA1c was analyzed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA1c as covariates. In Study H, there were 16.1% of subjects in the TRESIBA® and 14.5% insulin glargine arms for whom data was missing at the time of the HbA1c measurement.

14.4 Safety Outcomes Trial

DEVOTE (NCT01995929) Cardiovascular Outcomes Trial of TRESIBA® Administered Once-Daily Between Dinner and Bedtime in Combination with Standard of Care in Subjects with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease

DEVO was a multi-center, multi-national, randomized, double-blinded, active-controlled, treat-to-target, event-driven trial. 7,637 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to either TRESIBA® or insulin glargine U-100. Each was administered once-daily between dinner and bedtime in addition to standard of care diabetes and cardiovascular medications to achieve local standard of care treatment targets for lipids and blood pressure.

Cardiovascular Outcomes - Patients with T2DM and Atherosclerotic CVD

The incidence of major cardiovascular events with TRESIBA® was evaluated in DEVOTE. Subjects treated with TRESIBA® had a similar incidence of major adverse cardiovascular events (MACE) when compared to those treated with insulin glargine U-100. The primary endpoint in DEVOTE was time from randomization to the first occurrence of a 3-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

The study was designed to exclude a pre-specified risk margin for the hazard ratio of MACE comparing TRESIBA® to insulin glargine U-100. The primary outcome at end of trial was available for 98.2% of participants in each treatment group. The time to first occurrence of MACE with TRESIBA® was not captured in the trial.

At baseline, patients treated their diabetes with oral antidiabetic drugs (72%) and with an insulin regimen (84%). Types of insulins included long acting insulin (60%), intermediate acting insulin (14%) short acting insulin (37%) and premixed insulin (10%). 16% of patients were insulin naive. The most common background oral antidiabetic drugs used at baseline were metformin (60%), sulfonylureas (29%) and DPP-4 inhibitors (12%). During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets for lipids and blood pressure.
Table 15: Analysis of the Composite 3-point MACE and Individual Cardiovascular Endpoints in DEVOTE

<table>
<thead>
<tr>
<th>N</th>
<th>TRESIBA®</th>
<th>Insulin glargine U-100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3818</td>
<td>3819</td>
</tr>
<tr>
<td>Number of Patients (%)</td>
<td>Rate per 100 PYO</td>
<td>Rate per 100 PYO</td>
</tr>
<tr>
<td>325 (8.5)</td>
<td>4.41</td>
<td>356 (9.3)</td>
</tr>
</tbody>
</table>

Composite of first event of CV death, non-fatal MI, or non-fatal stroke: (3-Point MACE)

CV death: 136 (3.8) vs 143 (3.7)
Non-fatal MI: 144 (3.8) vs 169 (4.4)
Non-fatal stroke: 71 (1.9) vs 79 (2.1)

Hazard Ratio (95% CI) 0.91 [0.78; 1.06]

*PYO = patient-years of observation until first MACE, death, or trial discontinuation

Figure 3: Cumulative Event Probability for Time to First MACE in DEVOTE

Hypoglycemia Outcomes - Patients with T2DM and Atherosclerotic CVD

The pre-specified secondary endpoints of event and incidence rates of severe hypoglycemia were sequentially tested. Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucoin, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The incidence of severe hypoglycemia was lower in the TRESIBA® group as compared to the insulin glargine U-100 group (Table 16). Glycemic control between the two groups was similar at baseline and throughout the trial.

Table 16: Severe Hypoglycemic Episodes in Patients Treated with TRESIBA® or Insulin Glargine U-100 in DEVOTE

<table>
<thead>
<tr>
<th>N</th>
<th>TRESIBA®</th>
<th>Insulin glargine U-100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3818</td>
<td>3819</td>
</tr>
<tr>
<td>Severe Hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients with events</td>
<td>4.9%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Estimated odds ratio (95% CI)</td>
<td>TRESIBA®/Insulin glargine U-100</td>
<td>0.73 [0.60; 0.89]*</td>
</tr>
<tr>
<td>Events per 100 Patient Years of Observation</td>
<td>3.70</td>
<td>6.25</td>
</tr>
<tr>
<td>Estimated rate ratio (95% CI)</td>
<td>TRESIBA®/Insulin glargine U-100</td>
<td>0.60 [0.48; 0.76]*</td>
</tr>
</tbody>
</table>

* Test for superiority evaluated at 5% level for significance, (2-sided p<0.001)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRESIBA® injection is available as a clear and colorless solution in the following package sizes (see Table 17).

Table 17: Presentations of TRESIBA®

<table>
<thead>
<tr>
<th>TRESIBA® Presentation</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 single-patient-use FlexTouch® Pen</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-100 multiple-dose Vial</td>
<td>10 mL</td>
<td>100 units/mL</td>
<td>1,000 Units</td>
<td>0169-2662-11</td>
<td>–</td>
<td>–</td>
<td>1 vial/pack</td>
</tr>
<tr>
<td>U-200 single-patient-use FlexTouch® Pen</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>

TRESIBA® U-100 FlexTouch® dial in unit increments. TRESIBA® U-200 FlexTouch® dial in 2 unit increments.

16.2 Recommended Storage

Dispense in the original sealed carton with the enclosed Instructions for Use.
Do not share your TRESIBA® FlexTouch® insulin delivery device with other people, even if the needle has changed. Do not share needles or syringes with another person. You may give other people a serious infection, or get a serious infection from them.

What is TRESIBA®?
• TRESIBA® is a man-made insulin that is used to control high blood sugar in adults and children who are 1 year of age and older with diabetes mellitus.
• TRESIBA® is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
• It is not known if TRESIBA® is safe and effective in children under 1 year of age.
• TRESIBA® is available in 2 concentrations (U-100 and U-200):
  - U-100 concentration is available in pen and vial
  - The 100 units/mL pen can be injected from 1 to 80 units in a single injection, in increments of 1 unit.
  - The 100 units/mL vial should be used with a U-100 insulin syringe only.
  - U-200 concentration is only available in pen
  - The 200 units/mL pen can be injected from 2 to 160 units in a single injection, in increments of 2 units.

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

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

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

How should I take TRESIBA®?
• Read the Instructions for Use that come with your TRESIBA®.
• Take TRESIBA® exactly as your healthcare provider tells you to.
• Do not do any conversion of your dose. The dose counter always shows the selected dose in units. Both the 100 units/mL and 200 units/mL TRESIBA® FlexTouch® pens are made to deliver your insulin dose in units.
• Know the type and strength of insulin you take. Do not change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
• For children who need less than 5 units of TRESIBA® each day, use a TRESIBA® U-100 vial.
• Adults: If you miss or are delayed in taking your dose of TRESIBA®:
  - Take your dose as soon as you remember then continue with your regular dosing schedule.
  - Make sure there are at least 8 hours between your doses.
• If children miss a dose of TRESIBA®,
  - Call the healthcare provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of TRESIBA®.
• Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
• Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.
• Never inject TRESIBA® into a vein or muscle.
• Never use a syringe to remove TRESIBA® from the FlexTouch® pen.
• 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 with each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
  - Do not use the exact same spot for each injection.
  - Do not inject where the skin has pits, is thickened, or has lumps.
  - Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

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

What are the possible side effects of TRESIBA®?
TRESIBA® may cause serious side effects that can lead to death, including:
• Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - blurred vision
  - sweating
  - confusion
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - shakiness
  - headache
• 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
• 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, confused, a very weak or irregular heartbeat, or loss of consciousness
• slurred speech
• blurred vision
• fast heartbeat
• fainting
• sweating
• dizziness or light-headedness
• weakness or coldness in the hands or feet
• weight gain

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: glycerol, metacresol, phenol, water for injection, and zinc. 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: 11/2019
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, single-patient-use 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 it if it looks 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.

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

Steps 2-8:
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 tight (See Figure E).
Step 5: • Pull off the outer needle cap. Do not throw it away (See Figure F).
Step 6: • Pull off the inner needle cap and throw it away (See Figure G).
Step 7: • Turn the dose selector to select 2 units (See Figure H).
Step 8: • Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

Selecting your dose:
Step 10: TRESIBA® FlexTouch® Pen 200 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. Do not perform any dose conversion. Check to make sure the dose selector is set at 0.
• Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
• If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
• Each line on the dial is an even number.
• 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 60, 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 to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. Do not use the same injection site for each injection. Do not inject where the skin has pits, is thickened, or has lumps. Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Step 11:

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

(Figure M)

Step 12:

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

(Figure N)

Step 13:

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

(Figure Q)

Step 14:

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

(Figure O)

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.

(Figure R)

Step 16:

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

(Figure T)

After your injection:

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

How should I store my TRESIBA® FlexTouch® Pen?

Before use:

- Store unused TRESIBA® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze TRESIBA®. Do not use TRESIBA® if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA®:

- Keep TRESIBA® FlexTouch® Pens and needles out of the reach of children.
- Always use a new needle for each injection.
- Do not share TRESIBA® FlexTouch® Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
Revised: 11/2019
For more information go to www.TRESIBA.com

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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, single-patient-use pen containing 300 units of TRESIBA® (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.

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

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

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

NovoFine®

NovoTwist®

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 tight (See Figure E).

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

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

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

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

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

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

Check to make sure the dose selector is set at 0.
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The even numbers are printed on the dial.
  - The odd numbers are shown as lines.
- The TRESIBA® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).
  - To see how much insulin is left in your TRESIBA® FlexTouch® Pen:
    - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are at least 80 units left in your Pen.
    - If the dose counter shows less than 80, the number shown in the dose counter is the number of units left in your Pen.
Giving your injection:

- Inject your TRESIBA® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA® can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. Do not use the same injection site for each injection. Do not inject where the skin has pits, is thickened, or has lumps. Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

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 disposal 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 in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA® away from heat or light.
- The TRESIBA® FlexTouch® Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA®
- Keep TRESIBA® FlexTouch® Pens and needles out of the reach of children.
- Always use a new needle for each injection.
- Do not share TRESIBA® FlexTouch® Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.
Instructions for Use

TRESIBA® (tre–SI-bah) (insulin degludec injection) 10 mL multiple-dose vial (100 units/mL, U-100)

Read this Instructions for Use before you start taking TRESIBA® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The vial 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 and insulin syringe.

Do not reuse or share syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

Supplies you will need to give your TRESIBA® injection:

- a 10 mL TRESIBA® vial
- a U-100 insulin syringe and needle
- 2 alcohol swabs
- 1 sharps container for throwing away used syringes and needles. See “Disposing of your used needles and syringes” at the end of these instructions.

Preparing your TRESIBA® dose:

- Do not roll or shake the TRESIBA® vial. Shaking the TRESIBA® vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin.
- The tamper-resistant cap should not be loose or damaged before the first use. Do not use if the tamper-resistant cap is loose or damaged before using TRESIBA® for the first time.
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the TRESIBA® label to make sure that you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- Check that the TRESIBA® vial is not cracked or damaged. Do not use if the TRESIBA® vial is cracked or damaged.
- TRESIBA® should look clear and colorless. Do not use TRESIBA® if it is thick, cloudy, or is colored.
- Do not use TRESIBA® past the expiration date printed on the label or 56 days after you start using the TRESIBA® vial.

Step 1: Pull off the tamper-resistant cap (See Figure A).

Step 2: Wipe the rubber stopper with an alcohol swab (See Figure B).

Step 3: Hold the syringe with the needle pointing up. Pull down on the plunger until the tip of the plunger reaches the line for the number of units for your prescribed dose (See Figure C).

Step 4: Push the needle through the rubber stopper of the TRESIBA® vial (See Figure D).

Step 5: Push the plunger all the way in. This puts air into the TRESIBA® vial (See Figure E).

Step 6: Turn the TRESIBA® vial and syringe upside down and slowly pull the plunger down until the tip of the plunger is a few units past the line for your dose (See Figure F).

Step 7: Slowly push the plunger up to the tip of the plunger reaches the line for your prescribed TRESIBA® dose (See Figure G).

Step 8: Check the syringe to make sure you have the right dose of TRESIBA®.

Step 9: Pull the syringe out of the rubber stopper on the TRESIBA® vial (See Figure I).

Step 10: Choose your injection site and wipe the skin with an alcohol swab (See Figure J). Let the injection site dry before you inject your dose.

Step 11: Insert the needle into your skin. Push down on the plunger to inject your dose (See Figure K).

Step 12: Pull the needle out of your skin. After your injection, you may see a drop of TRESIBA® at the needle tip. This is normal and does not affect the dose you just received (See Figure L).

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

After your injection:

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

Disposing of your used needles and syringes:

Put your used insulin needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- properly labeled to warn of hazardous waste inside the container.
- leak-resistant
- 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
- 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 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.

Giving your TRESIBA® 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® (insulin degludec injection) 10 mL vial

- 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 TRESIBA®?

Before use:
- Store unopened TRESIBA® vials in the refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- Do not freeze TRESIBA®. Do not use TRESIBA® if it has been frozen.
- Unused TRESIBA® vials may be used until the expiration date printed on the label, if they are kept in the refrigerator.
- After 56 days, throw away TRESIBA® vials that have been kept at room temperature (below 86°F (30°C)).

Vial in use:
- Store the TRESIBA® vial you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C) in the original carton to protect from light.
- Keep TRESIBA® away from direct heat or light.
- The TRESIBA® vial 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® vials, syringes, and needles out of the reach of children.
- Always use a new syringe and needle for each injection to help ensure sterility and prevent blocked needles.
- Do not reuse or share syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.