PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TRESIBA®

insulin degludec injection

TRESIBA® Penfill® 100 U/mL, Solution for injection in a cartridge

TRESIBA® FlexTouch® 100 U/mL, Solution for injection in a pre-filled pen

TRESIBA® FlexTouch® 200 U/mL, Solution for injection in a pre-filled pen

Subcutaneous

Antidiabetic Agent

Long-Acting Basal Insulin Analogue

ATC Code: A10AE06

Novo Nordisk Canada Inc.

101-2476 Argentia Road

Mississauga, Ontario

Canada L5N 6M1

Date of Initial Authorization:
AUG 25, 2017

Date of Revision:
OCT 27, 2022

Submission Control Number: 258642

RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	03/2021
7 Warnings and Precautions, 7.11 Pregnant Women	10/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRESIBA® is indicated for once-daily treatment of adults with diabetes mellitus to improve glycemic control.

1.1 Pediatrics

Pediatrics (≥2 years old): TRESIBA® is also indicated for the treatment of pediatric patients (≥2 years old) with Type 1 diabetes mellitus.

TRESIBA® has not been investigated in pediatric patients with type 2 diabetes mellitus. The safety and efficacy of TRESIBA® has not been established in pediatric patients less than 2 years of age with type 1 diabetes mellitus.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall clinical differences in safety or effectiveness have been observed between elderly and adult patients.

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

2 CONTRAINDICATIONS

Insulin degludec is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING.

- During episodes of hypoglycemia (see 5 OVERDOSAGE)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products including Tresiba®. As with all insulin products the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with diabetes mellitus treated with TRESIBA® (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia).
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, and death.
- Changes in insulin regimen from other insulins to Tresiba®can cause serious hypoglycemia or hyperglycemia; changes should be made cautiously and only under medical supervision (see 6 DOSAGE AND ADMINISTRATION).

- Inspect Tresiba® visually prior to administration and use only if the solution appears clear and colourless.
- Never mix Tresiba® with any other insulin.
- Never administer Tresiba® intravenously (IV) or with an insulin infusion pump

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Tresiba® is for subcutaneous use only.
- DO NOT administer Tresiba® intravenously as it may result in severe hypoglycemia.
- DO NOT administer Tresiba® intramuscularly as it may change the absorption.
- DO NOT administer Tresiba® in an insulin infusion pump.
- Inspect visually for particulate matter and discolouration. Only use Tresiba® if the solution appears clear and colourless.
- Patients must visually check the Tresiba® label and verify the correct dialed dosage units on the delivery device before each injection, to avoid accidental medication errors (e.g., overdose and hypoglycemia). Instruct patients who are blind or have poor vision to always get assistance from another person who has good vision and is trained in using the delivery device.
- The potency of insulin analogues, including insulin degludec, is expressed in units (U). One (1) unit (U) insulin degludec corresponds to one international unit (IU) of human insulin, 1 unit of insulin glargine 100 U/mL or 1 unit of insulin detemir.
- Tresiba® is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Always rotate injection sites within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Tresiba®should not be injected into areas of lipodystrophy or localized cutaneous amyloidosis (see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS).
- Use Tresiba® with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- DO NOT perform dose conversion when using the Tresiba® U-100 or U-200 FlexTouch® pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

Tresiba® is a long-acting basal insulin for once-daily subcutaneous administration at any time of

day.

In patients with type 2 diabetes mellitus, Tresiba®can be used in combination with:

- oral antidiabetic agents (OADs), when treatment with OADs does not achieve adequate glycemic control.
- rapid-acting or short-acting insulin with or without metformin, when basal, basal-bolus or premix insulin therapy with or without metformin do not achieve adequate glycemic control.

Tresiba® has not been studied in combination with all OAD combinations (see 14 CLINICAL TRIALS).

In patients with type 1 diabetes mellitus, Tresiba®must be used in regimens containing rapid-acting or short-acting insulin to cover mealtime insulin requirements.

4.2 Recommended Dose and Dosage Adjustment

Inject Tresiba® subcutaneously once-daily at any time of day.

The dosage of Tresiba®should be individualized and titrated under the supervision of a health care provider in accordance with the metabolic needs of the patient and the glycemic control target and with appropriate glucose monitoring.

Blood glucose monitoring is essential in all patients receiving insulin therapy (see 7 WARNINGS AND PRECAUTIONS).

Dose adjustments may be needed with changes in physical activity, changes in meal patterns, changes in renal or hepatic function or during acute illness, to minimize the risk of hypoglycemia or hyperglycemia.

Geriatric patients (>65 years of age):

No dosage adjustment is recommended in the geriatric population. Caution is warranted when Tresiba®is administered to geriatric patients since greater sensitivity of some older individuals to the effects of Tresiba®cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia, which may be particularly difficult to recognize in the elderly.

Pediatric patients (2-18 years of age) with type 1 diabetes:

Tresiba® can be used in adolescents and children with type 1 diabetes from the age of 2 years. Inject Tresiba® subcutaneously once-daily at approximately the same time of the day. When changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimize the risk of hypoglycemia. A 20% dose reduction is recommended when initiating Tresiba® in pediatric patients in order to minimize the risk of hypoglycemia.

Patients with renal impairment:

No dosage adjustment is recommended in subjects with mild, moderate, or severe renal impairment. In patients with renal impairment, glucose monitoring should be intensified and Tresiba® dosage adjusted on an individual basis as necessary.

Patients with hepatic impairment:

No dosage adjustment is recommended in subjects with mild, moderate, or severe hepatic impairment. In patients with hepatic impairment, glucose monitoring should be intensified and Tresiba®dosage adjusted on an individual basis as necessary.

Initiation of Tresiba® Therapy in Insulin Naïve Patients

Adult and pediatric patients with type 1 diabetes mellitus

Tresiba® is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments. 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.

Adult patients with type 2 diabetes mellitus

The recommended starting dose of Tresiba® in insulin naïve patients with type 2 diabetes mellitus is 10 units once daily.

Initiation of Tresiba® Therapy in Patients Changing from Other Insulin Therapies

Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Adult and pediatric patients with type 1 diabetes mellitus

For patients with type 1 diabetes, it is recommended that the dose of Tresiba® is reduced by 20% from the total daily long- or intermediate-acting insulin dose, or basal component of a continuous subcutaneous insulin infusion regimen, to lower the risk of hypoglycemia. The amount and timing of the prandial insulin may need to be adjusted as well.

Adult patients with type 2 diabetes mellitus

For patients with type 2 diabetes taking once-daily long or intermediate-acting insulin, start Tresiba® at the same unit dose. For patients transferring from twice daily long or intermediate-acting insulin, or insulin glargine (300 units/mL), it is recommended that the dose of Tresiba® is reduced by 20% to lower the risk of hypoglycemia.

4.4 Administration

Refer to the instructions provided at the end of this Product Monograph in the section "Instructions on How to Use Tresiba® 100/200 units/mL Solution for Injection in Pre-filled Pen" for information on Tresiba® FlexTouch®.

For Tresiba® Penfill®, refer to the instructions provided with your Novo Nordisk Insulin Delivery Device manual.

4.5 Missed Dose

Instruct patients who miss a dose of Tresiba® to inject their daily dose upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive Tresiba® injections.

5 OVERDOSAGE

A specific overdose for insulin cannot be defined. However, hypoglycemia may develop over sequential stages if a patient is dosed with more insulin than required (see 7 WARNINGS AND PRECAUTIONS).

Mild hypoglycemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carry glucose-containing products.

Severe hypoglycemic episodes, where the patient is not able to treat themselves, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution for injection / 100 U/mL and 200 U/mL	Glycerol, metacresol, phenol, water for injection and zinc acetate .

Dosage Forms: Tresiba® (insulin degludec injection) is available in the following package sizes. Each presentation contains 100 Units of Tresiba® per mL (U-100) or 200 Units of Tresiba® per mL (U-200).

TRESIBA®	Total volume	Strength	Total units available in presentation	Max dose per injection*	Dose increment*	Pack Size
U-100 FlexTouch®	3 mL	100 U/mL	300 U	80 U	1 U	1 x 3 mL 5 x 3 mL
U-200 FlexTouch®	3 mL	200 U/mL	600 U	160 U	2 U	1 x 3 mL 3 x 3mL
U-100 Penfill®	3 mL	100 U/mL	300 U			5 x 3 mL

*For Penfill®, max dose and dose increment depends on the 3mL Penfill® cartridge insulin delivery device used.

Composition: Tresiba® (insulin degludec injection) 100 Units/mL (U-100) or 200 Units/mL (U-200) and inactive ingredients are glycerol, phenol, metacresol, zinc acetate and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

All Tresiba® Penfill® cartridges and Tresiba® FlexTouch® are latex-free.

Packaging: Penfill® 3 mL cartridge is made of glass (type 1), containing a halobutyl rubber closure shaped as a plunger and closed with a halobutyl/polyisoprene laminate rubber sheet. The cartridges are packed in a carton.

FlexTouch®: Pre-filled pen (multidose disposable pen) comprising a pen-injector with a cartridge (3 mL). The cartridge is made of glass (type 1), containing a halobutyl rubber closure shaped as a plunger and closed with a halobutyl/polyisoprene laminate rubber sheet.

Description

Tresiba® (insulin degludec injection) is a long-acting basal insulin analogue with a duration of action over 42 hours used to lower blood glucose. Insulin degludec is produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification.

7 WARNINGS AND PRECAUTIONS

Please see the 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

When using Tresiba® (insulin degludec injection) in combination with oral anti-diabetic agents (OADs) please refer to the respective product monograph for OADs for their 7 WARNINGS AND PRECAUTIONS information.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirement. In these instances, patients should contact their physician and carefully control their blood glucose.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph 7 WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including Tresiba®, is contemplated.

Patients should never share insulin delivery devices, including a Tresiba® FlexTouch® disposable prefilled pen, a Tresiba® Penfill®, or a Novo Nordisk Insulin Delivery Device, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Tresiba® should not be diluted or mixed with any other insulin product.

Endocrine and Metabolism

Hypoglycemia: Hypoglycemia is the most common adverse reaction of all insulin preparations, including Tresiba® (see 8 ADVERSE REACTIONS). Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). Tresiba®, or any insulin, should not be used during episodes of hypoglycemia (see 2 CONTRAINDICATIONS).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) (see 9 DRUG INTERACTIONS), or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia
The timing of hypoglycemia usually reflects the duration of action of the administered insulin formulation and, in general, is highest when the glucose-lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of Tresiba® may vary among different individuals or at different times in the same individual and depends on many conditions, including both the blood supply and temperature at the injection site.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication (see 9 DRUG INTERACTIONS). Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

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

Hypoglycemia Due to Medication Errors
Accidental mix-ups between basal insulin products, different strengths and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors with Tresiba® and other insulins, instruct patients to always visually check the product label before each injection.

Do not transfer Tresiba® from the Tresiba® pen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia.

Hypoglycemia Due to Changes in Insulin Regimen
Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed (see 4 DOSAGE AND ADMINISTRATION).

Hyperglycemia: Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycemia and thereby cause an increased insulin requirement.

Usually, the first symptoms of hyperglycemia develop gradually over a period of hours or days. They can include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite, and acetone odour of breath. In patients with type 1 diabetes mellitus, untreated hyperglycemic events eventually lead to diabetic ketoacidosis, which can cause death.

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed (see 4 DOSAGE AND ADMINISTRATION).

Hypokalemia: Hypokalemia is among the potential clinical adverse effect associated with the use of all insulins therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhea) (See 8 ADVERSE REACTIONS). Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Hepatic/Biliary/Pancreatic

Tresiba® can be used in hepatic impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see 10 CLINICAL PHARMACOLOGY).

Immune

Lipodystrophy and Cutaneous Amyloidosis:

SC administration of insulin products, including Tresiba® can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (thickening of adipose tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Hypersensitivity and allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Tresiba®. If hypersensitivity reactions occur, discontinue Tresiba®; treat per standard of care and monitor until symptoms and signs resolve. Tresiba® is contraindicated in patients who have had hypersensitivity reactions to insulin degludec or one of the excipients (see 2 CONTRAINDICATIONS).

Antibody Production: Insulin administration may cause the production of insulin antibodies. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose to minimize the development of hyper- or hypoglycemia.

Monitoring and Laboratory Tests

As with all insulin therapy, the therapeutic response to Tresiba® should be monitored by periodic blood glucose tests. Glycosylated hemoglobin should be measured every 3 to 4 months in all patients taking insulin.

Renal

Tresiba® can be used in renal impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see CLINICAL PHARMACOLOGY).

In the safety outcomes trial (DEVOTE), a total of 1429 (37.4%) of the 3818 Tresiba®-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m^2, and 108 (2.8%) subjects had an eGFR less than 30 mL/min/1.73 m^2. Differences in safety or effectiveness were not observed in the subgroup analyses.

7.1 Special Populations

7.1.1 Pregnant Women

Treatment with Tresiba® can be considered during pregnancy, if the benefit justifies possible risks and if clinically needed. The use of Tresiba® in pregnant women with diabetes has been investigated in an interventional trial (see 8.2 Clinical Trial Adverse Reactions, 14 CLINICAL TRIALS). Available data from the study did not identify a drug-associated risk of major birth defects. In about two thirds of infants in the interventional trial, insulin degludec was detected in the infant cord blood at levels above the lower level of quantification of the assay.

In the clinical study, no perinatal or neonatal death was reported. No clinically relevant differences were observed between Tresiba® and insulin detemir for the pregnancy endpoints (early fetal death, presence of major abnormalities, neonatal hypoglycemia, perinatal mortality, neonatal mortality, fetal macrosomia, large for gestational age, and adverse events in the infant during the 30 days after birth) (see 8.2 Clinical Trial Adverse Reactions). Animal developmental toxicity studies have indicated that the effect of insulin degludec was consistent with those observed with human insulin, as both resulted in pre- and post-implantation losses and skeletal malformations and variations in rats at an insulin degludec dose approximately 5 times the human exposure (AUC) and in rabbits at approximately 10 times the human exposure (see 16 NON-CLINICAL TOXICOLOGY). Animal reproduction studies are not always predictive of human response. In general, intensified blood glucose control and careful monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

7.1.2 Breast-feeding

There is no clinical experience from well-controlled studies with Tresiba® during breast-feeding. It is unknown whether insulin degludec is excreted in human milk. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma.

7.1.3 Pediatrics

The safety and efficacy of Tresiba® to improve glycemic control has been established in pediatric patients 2 years of age and older with type 1 diabetes mellitus (see 14 CLINICAL TRIALS, Study demographics and trial design, Type 1 Diabetes Mellitus). The safety and efficacy of Tresiba® has not been established in pediatric patients less than 2 years of age with type 1 diabetes mellitus.

When changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimize the risk of hypoglycemia. A 20% dose reduction is recommended when initiating Tresiba® in pediatric patients in order to minimize the risk of hypoglycemia (see 4 DOSAGE AND ADMINISTRATION).

7.1.4 Geriatrics

In controlled adult therapeutic confirmatory trials a total of 77 (7%) of the 1102 Tresiba® - treated subjects with type 1 diabetes were 65 years or older and from those 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.

In the safety outcomes trial (DEVOTE), a total of 1983 (52%) 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.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Type 1 and type 2 diabetes in adults:

The safety of Tresiba® was primarily evaluated in 11 phase 3a clinical trials, including three trials in patients with type 1 diabetes mellitus (T1DM) and eight trials in patients with type 2 diabetes mellitus (T2DM). In the phase 3 clinical program, 6206 subjects were exposed to Tresiba®, while 2717 subjects were exposed to comparator; this corresponded to 5345 and 2054 patient-years-exposure (PYE), respectively. The majority of subjects exposed to TRESIBA® (n=5104; 82%) were classified as having type 2 diabetes mellitus (T2DM), with a marginally greater distribution of insulin-naïve subjects (n=2911; 57%) relative to other insulin-treated subjects (n=2193; 43%) with T2DM.

Hypoglycemia was the most frequently observed adverse event; however, only hypoglycemic events classified as severe events requiring assistance from another person were reported as an AE. Viral upper respiratory tract infection, upper respiratory tract infection, headache, and diarrhea were the most frequently reported AEs. Hypoglycemic events were the most frequently reported serious and severe AEs. Medication errors – including serious and/or severe events – were more frequently reported in patients exposed to Tresiba® compared to comparator. Hypoglycemia, weight increased, and major adverse cardiovascular events were the most frequently reported AEs leading to treatment withdrawal. The majority of AEs were considered to be tolerable, reversible, and self-limiting.

Type 1 diabetes in children and adolescents:

The safety of Tresiba® has been studied in an open-label therapeutic confirmatory trial in pediatric subjects 1 year of age and older (12 months duration) with type 1 diabetes.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The therapeutic confirmatory trials were randomized, controlled, parallel-group, open-label, multicentre, multinational, treat-to-target trials in which Tresiba® was compared to an active comparator. Overall, 4449 subjects were exposed to Tresiba® and 2444 subjects were exposed to comparators, corresponding to 2989.6 and 1486.5 patient-years exposure (PYE), respectively. In these trials, 3928 (88%) subjects had at least 6 months exposure to Tresiba®, while 1804 (40%) subjects were exposed to Tresiba® for at least 12 months.

In subjects with type 1 diabetes mellitus (including pediatrics), 1276 were exposed to Tresiba® and 642 were exposed to comparators, corresponding to 888.2 and 442.3 PYE, respectively. Subjects were most frequently white (80.3%), males (56.3%), with a mean age of 37.6 years. Subjects had a mean BMI of 24.8 kg/m2, a mean duration of diabetes of 15.6 years, a baseline mean HbA_{1c} of 7.8%, and a baseline mean fasting plasma glucose level of 9.5 mmol/L.

In subjects with type 2 diabetes mellitus, 3173 were exposed to Tresiba® and 1802 were exposed to comparators, corresponding to 2101.4 and 1044.2 PYE, respectively. Subjects were most frequently white (73.1%), males (56.5%), with a mean age of 57.9 years. Subjects had a mean BMI of 30.9 kg/m2, a mean duration of diabetes of 10.2 years, a baseline mean HbA_{1c} of 8.3%, and a baseline mean fasting plasma glucose level of 9.4 mmol/L.

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 14 CLINICAL TRIALS).

The safety of Tresiba® in 91 adult women with type 1 diabetes between weeks 8 and 13 of gestation or who intend to become pregnant was also evaluated in one randomized, open-label, treat-to-target, active-controlled trial.

Adverse Reactions in Type 1 (including pediatrics) and Type 2 Diabetes Mellitus Trials

Treatment-emergent adverse events reported from the therapeutic confirmatory trials regardless of relatedness to trial drug occurring at a rate of ≥ 2% in subjects with type 1 diabetes mellitus (Table 1 and Table 2) or type 2 diabetes mellitus (Table 3) are provided.

Table 1-1: Treatment-emergent adverse events occurring in ≥2% of adult subjects, in any group, with Type 1 diabetes

Preferred term	Tresiba® (n=1102) (%)	Comparator (n=467) (%)
Gastrointestinal disorders		

Preferred term	Tresiba® (n=1102) (%)	Comparator (n=467) (%)
Nausea	52 (4.7%)	21 (4.5%)
Diarrhea	45 (4.1%)	23 (4.9%)
Vomiting	43 (3.9%)	14 (3.0%)
Abdominal pain upper	23 (2.1%)	10 (2.1%)
General disorders and administration site conditions		
Pyrexia	24 (2.2%)	12 (2.6%)
Fatigue	19 (1.7%)	10 (2.1%)
Immune system disorders		
Seasonal allergy	12 (1.1%)	12 (2.6%)
Infections and infestations		
Viral upper respiratory tract infection	265 (24.0%)	105 (22.5%)
Upper respiratory tract infection	131 (11.9%)	47 (10.1%)
Sinusitis	56 (5.1%)	23 (4.9%)
Gastroenteritis	56 (5.1%)	15 (3.2%)
Influenza	46 (4.2%)	20 (4.3%)
Urinary tract infection	40 (3.6%)	10 (2.1%)
Bronchitis	33 (3.0%)	15 (3.2%)
Gastroenteritis viral	24 (2.2%)	11 (2.4%)
Rhinitis	18 (1.6%)	10 (2.1%)
Injury, poisoning and procedural complications		
Wrong drug administered	53 (4.8%)	14 (3.0%)
Metabolism and nutrition disorders		
Hypoglycemia*	99 (9.0%)	37 (7.9%)
Musculoskeletal and connective tissue disorders		
Back pain	45 (4.1%)	15 (3.2%)
Arthralgia	30 (2.7%)	8 (1.7%)
Pain in extremity	29 (2.6%)	7 (1.5%)
Nervous system disorders		
Headache	130 (11.8%)	49 (10.5%)
Hypoglycemic unconsciousness	36 (3.3%)	13 (2.8%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	52 (4.7%)	28 (6.0%)
Cough	47 (4.3%)	29 (6.2%)
Nasal congestion	13 (1.2%)	11 (2.4%)

* AEs were restricted to events of severe hypoglycemia. Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Table 1-2: Treatment-emergent adverse events occurring in ≥2% of pediatric subjects, in any group, with Type 1 diabetes

Preferred term	Pediatrics (52 weeks)	
	Tresiba® (n=174) (%)	IDet (n=175) (%)
Ear and labyrinth disorders		
Ear pain	10 (5.7%)	5 (2.9%)

Preferred term	Pediatrics (52 weeks)	
	Tresiba® (n=174) (%)	**IDet (n=175) (%)**
Gastrointestinal disorders		
Abdominal pain	12 (6.9%)	8 (4.6%)
Abdominal discomfort	8 (4.6%)	4 (2.3%)
Constipation	5 (2.9%)	6 (3.4%)
Dental caries	2 (1.1%)	4 (2.3%)
Dyspepsia	2 (1.1%)	17 (9.7%)
General disorders and administration site conditions		
Injection site reaction	7 (4.0%)	3 (1.7%)
Malaise	6 (3.4%)	3 (1.7%)
Injection site pain	4 (2.3%)	
Infections and infestations		
Ear infection	9 (5.2%)	11 (6.3%)
Tonsillitis	8 (4.6%)	9 (5.1%)
Nasopharyngitis	7 (4.0%)	7 (4.0%)
Gastroenteritis viral infection	6 (3.4%)	1 (0.6%)
Pharyngitis	6 (3.4%)	10 (5.7%)
Viral infection	6 (3.4%)	10 (5.7%)
Otitis media	5 (2.9%)	4 (2.3%)
Conjunctivitis	4 (2.3%)	3 (1.7%)
Paronychia	4 (2.3%)	2 (1.1%)
Viral rash	4 (2.3%)	
Gastrointestinal infection	2 (1.1%)	4 (2.3%)
Varicella	1 (0.6%)	4 (2.3%)
Injury, poisoning and procedural complications		
Ligament sprain	6 (3.4%)	5 (2.9%)
Fall	4 (2.3%)	1 (0.6%)
Laceration	4 (2.3%)	3 (1.7%)
Limb injury	4 (2.3%)	1 (0.6%)
Sports injury	4 (2.3%)	1 (0.6%)
Accidental overdose	1 (0.6%)	5 (2.9)
Investigations		
Blood ketone body increased	31 (17.8%)	46 (26.3%)
Nervous system disorders		
Dizziness	4 (2.3%)	4 (2.3%)
Hypoglycaemic seizure	4 (2.3%)	5 (2.9%)
Respiratory, thoracic and mediastinal disorders		
Rhinorrhoea	6 (3.4%)	6 (3.4%)
Respiratory disorder	4 (2.3%)	7 (4.0%)
Sinus congestion	5 (2.9%)	2 (1.1%)
Skin and subcutaneous tissue disorders		
Rash	5 (2.9%)	1 (0.6%)
Eczema	4 (2.3%)	3 (1.7%)
Lipohypertrophy	4 (2.3%)	2 (1.1%)

Table 1-3: Treatment-emergent adverse events occurring in ≥2% of adults with Type 2 diabetes

Preferred term	Tresiba® (n=3173) (%)	Comparator (n=1802) (%)
Eye disorders		
Diabetic retinopathy	69 (2.2%)	37 (2.1%)
Gastrointestinal disorders		
Diarrhea	197 (6.2%)	129 (7.2%)
Nausea	105 (3.3%)	74 (4.1%)
Vomiting	79 (2.5%)	51 (2.8%)
General disorders and administration site conditions		
Fatigue	73 (2.3%)	42 (2.3%)
Edema peripheral	71 (2.2%)	27 (1.5%)
Infections and infestations		
Viral upper respiratory tract infection	382 (12.0%)	175 (9.7%)
Upper respiratory tract infection	242 (7.6%)	127 (7.0%)
Bronchitis	113 (3.6%)	49 (2.7%)
Influenza	105 (3.3%)	44 (2.4%)
Urinary tract infection	80 (2.5%)	38 (2.1%)
Sinusitis	76 (2.4%)	40 (2.2%)
Gastroenteritis	70 (2.2%)	40 (2.2%)
Musculoskeletal and connective tissue disorders		
Back pain	153 (4.8%)	83 (4.6%)
Pain in extremity	108 (3.4%)	59 (3.3%)
Arthralgia	105 (3.3%)	56 (3.1%)
Muscle spasms	64 (2.0%)	24 (1.3%)
Nervous system disorders		
Headache	278 (8.8%)	121 (6.7%)
Dizziness	66 (2.1%)	57 (3.2%)
Respiratory, thoracic and mediastinal disorders		
Cough	136 (4.3%)	56 (3.1%)
Oropharyngeal pain	79 (2.5%)	35 (1.9%)
Vascular disorders		
Hypertension	105 (3.3%)	43 (2.4%)

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including Tresiba®. 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. Comparing rates of hypoglycemia between products may therefore, be misleading and not representative of rates to be expected in clinical practice.

Hypoglycemic episodes reported as adverse events were restricted to events of severe hypoglycemia. Severe hypoglycemia in these open-label adult T1DM and T2DM therapeutic confirmatory trials was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia in the pediatric trial was defined as an altered mental status where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose). Events of confirmed hypoglycemia were

defined as episodes of severe hypoglycemia and episodes of hypoglycemia with a plasma glucose value <3.1 mmol/L irrespective of symptoms.

Percentages of adult and pediatric patients randomized to Tresiba® who experienced at least one episode of hypoglycemia and the hypoglycemic event rates are shown in Tables 1-4 and 1-5, respectively. Clinically important differences in the risk of hypoglycemia between Tresiba® and comparators have not been established in these clinical trials.

Table 1-4: Percent (%) of Type 1 Diabetes Patients Experiencing at least One Episode of Severe Hypoglycemia or Confirmed Hypoglycemia on TRESIBA® and Event Rates in Open-Label Adult and Pediatric Therapeutic Confirmatory Trials**

	Trial A + Insulin aspart 52 weeks	**Trial B + Insulin aspart 26 weeks**	**Trial C + Insulin aspart 26 weeks**		**Trial D Pediatrics + Insulin aspart 52 weeks**	**EXPECT (4300) - Pregnant Adults + Insulin aspart**
	Tresiba® (N=472)	Tresiba® (N=301)	Tresiba® at the same time each day (N=165)	Tresiba® at alternating times (N=164)	Tresiba® (N=174)	Tresiba® (N=91)
Severe hypoglycemia*						
Percent of patients	12.3%	10.6%	12.7%	10.4%	17.8%	5.5%
Events per patient year	0.21	0.31	0.37	0.34	0.51	0.22
Confirmed hypoglycemia**						
Percent of patients	95.6%	93.0%	99.4%	93.9%	98.3%	86.8%
Events per patient year	42.54	45.83	88.25	82.38	65.60	43.84

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

**Confirmed hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 3.1 mmol/L or where a whole blood glucose was less than 2.8 mmol/L i.e., with or without the presence of hypoglycemic symptoms.

Table 1-5: Percent (%) of Type 2 Diabetes Patients Experiencing at least One Episode of Severe Hypoglycemia or Confirmed Hypoglycemia* on TRESIBA® and Event Rates in Open-Label Adult Therapeutic Confirmatory Trials

	Trial E + 1-2 OADs** Insulin naïve 52 weeks	Trial F + 1-2 OAD**s Insulin naïve 26 weeks	Trial G T2DM ± 0-3 OADs** 26 weeks		Trial H T2DM ± 0-2 OADs** + Insulin aspart 26 weeks
	Tresiba® (N=766)	Tresiba® (N=228)	Tresiba® (N=226)	Tresiba® (alternating time) (N=230)	Tresiba® (N=753)
Severe hypoglycemia					
Percent of patients	0.3%	0	0.9%	0.4%	4.5%
Events per patient year	0	0	0.02	0.02	0.06
Confirmed hypoglycemia*					
Percent of patients	46.5%	28.5%	43.8%	50.9%	80.9%
Events per patient year	1.52	1.52	3.63	3.64	11.09

*Confirmed hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 3.1 mmol/L or where a whole blood glucose was less than 2.8 mmol/L i.e., with or without the presence of hypoglycemic symptoms.

** OAD: oral antidiabetic agent

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 7 WARNINGS AND PRECAUTIONS). Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were rarely reported in 0.9% of patients treated with Tresiba® in therapeutic confirmatory adult trials.

Skin and subcutaneous tissue disorder

Long-term use of insulin, including Tresiba®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue), lipoatrophy (thinning of adipose tissue), and cutaneous amyloidosis may delay insulin absorption (see 4 DOSAGE AND ADMINISTRATION). In therapeutic confirmatory adult trials, lipodystrophy and lipohypertrophy were rare and 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 therapeutic confirmatory adult and pediatric trials, injection site reactions occurred rarely in patients treated with Tresiba®.

Weight Gain

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

Peripheral Edema

Insulin, including Tresiba®, may cause sodium retention and edema. In therapeutic confirmatory adult trials, peripheral edema occurred in 0.9% of patients with type 1 diabetes mellitus and 3.0% of patients with type 2 diabetes mellitus treated with Tresiba®.

Immunogenicity

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

In studies of type 1 diabetes patients, 95.9% of patients who received Tresiba® once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7% that were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received Tresiba® once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

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

Use in Pregnancy

Tresiba® has been studied in an open-label, randomized, active controlled clinical trial (EXPECT) in which pregnant women with type 1 diabetes mellitus were treated within a basal-bolus treatment regimen with Tresiba® (n=92) or insulin detemir (n=96) as basal insulin, both in combination with insulin aspart as mealtime insulin (see 14 CLINICAL TRIALS). Mean exposure time during pregnancy was 182.5 days (range 7-266 days) for Tresiba® and 175.0 days (range 11-270 days) for insulin detemir. Pregnancies resulted in live births for 86 (93.5%) Tresiba® and 85 (88.5%) insulin detemir subjects.

There were no clinically relevant differences between the Tresiba® and insulin detemir arms in terms of maternal (11383.0 events per 100 Tresiba® vs. 14501.9 events per 100 PYE insulin detemir; Table 1-4) or neonatal hypoglycemia (23.3% Tresiba®, 22.4% insulin detemir), adverse events during pregnancy (85.7% Tresiba®, 80.9% insulin detemir), neonatal adverse events (59.3% Tresiba®, 60.6% insulin detemir), early fetal death (5.4% Tresiba®, 7.3% insulin detemir), or major congenital abnormalities (8.7% Tresiba®, 8.3% insulin detemir). There were no maternal, perinatal, or neonatal deaths.

Pregnant women treated with Tresiba® had higher incidences of serious adverse events

(41.8% Tresiba®, 34.0% insulin detemir), severe adverse events (11.0% Tresiba®, 6.4% insulin detemir), dose reductions due to adverse events (13.2% Tresiba®, 8.5% insulin detemir), preeclampsia (13.2% Tresiba®, 7.4% insulin detemir), preterm delivery (37.0% Tresiba, 27.1% insulin detemir), and non-planned caesarean section (25.3% Tresiba®, 16.0% insulin detemir). It is unclear whether the higher incidences of such events were attributable to differences between groups in terms of pregnancy complexity or maternal characteristics.

In about two thirds of infants, insulin degludec was detected in the infant cord blood at levels above the lower level of quantification of the assay.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Reactions <1%

Adult Subjects (Type 1 and Type 2 diabetes):

Ear and labyrinth disorders: Vertigo

Eye disorders: Vision blurred, maculopathy, retinal hemorrhage

Gastrointestinal disorders: Abdominal distension, abdominal discomfort, flatulence, dyspepsia

General disorders and administration site conditions: Injection site reaction (pain, pruritus, erythema, nodule, hematoma, hemorrhage), edema, hunger

Injury, poisoning and procedural complications: Incorrect dose administered, accidental overdose

Metabolism and nutrition disorders: Hyperglycemia, hypoglycemia unawareness, decreased appetite, increased appetite, obesity

Nervous system disorders: Hypoglycemic coma, tremor, diabetic neuropathy, neuropathy peripheral, migraine, lethargy, somnolence

Psychiatry disorders: Insomnia

Respiratory, thoracic and mediastinal disorders: Dyspnea

Skin and subcutaneous tissue disorders: Hyperhidrosis, dermatitis, eczema, pruritus, rash, lipohypertrophy, urticaria

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Pediatric Subjects (Type 1 diabetes):

Gastrointestinal disorders: Vomiting

General disorders and administration site conditions: Injection site (bruising, erythema, hemorrhage, rash), pyrexia

Immune system disorders: Seasonal allergy

Injury, poisoning and procedural complications: Incorrect dose administered

Investigations: Blood glucose increased

Metabolism and nutrition disorders: Decreased appetite

Musculoskeletal and connective tissue disorders: Back pain, musculoskeletal pain

Nervous system disorders: Headache, presyncope

Psychiatry disorders: Anxiety, initial and middle insomnia

Respiratory, thoracic and mediastinal disorders: Cough, wheezing

Skin and subcutaneous tissue disorders: Urticaria

8.5 Post-Market Adverse Reactions

Medication errors (including accidental mix-ups between Tresiba® and other insulin products, and between different strengths of Tresiba®) have been reported during post marketing use of Tresiba®. Since post-marketing data is reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to the drug.

Medication error. (see 7 WARNINGS AND PRECAUTIONS, Hypoglycemia Due to Medication Errors)

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

A number of medications affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood-glucose-lowering effect of Tresiba® and susceptibility to hypoglycemia:
Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), sulfonamide antibiotics, GLP-1 receptor agonists, DDP-4 inhibitors, SGLT-2 inhibitors.

Drugs that may reduce the blood-glucose-lowering effect of Tresiba®:
Corticosteroids, danazol, diuretics, glucagon, isoniazid, niacin, phenothiazine derivatives, oral contraceptives, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, salbutamol, terbutaline), thyroid hormones, and atypical antipsychotics (e.g., olanzapine and clozapine).

Drugs or substances may increase or decrease the blood-glucose-lowering effect of Tresiba®:
Beta-blockers, clonidine, lithium salts, and alcohol.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Sympatholytic medicinal products, such as beta-blockers, clonidine, guanethidine, and reserpine, may mask the symptoms of hypoglycemia (i.e. the signs and symptoms of hypoglycemia may be reduced or absent).

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia (see 5 OVERDOSAGE).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin degludec to circulating albumin.

10.2 Pharmacodynamics

The glucose-lowering effect of Tresiba® was evaluated using the euglycemic glucose clamp technique. Figure 1-1 shows the pharmacodynamics effect of Tresiba® over time at steady state following 8 once-daily subcutaneous injections of 0.4 U/kg of Tresiba® in 21 patients with type 1 diabetes. The mean maximum glucose lowering effect (GIRmax) was observed at a median of 12 hours and the duration of glucose lowering effect lasted beyond 42 hours after the last of 8 days of once-daily injections.

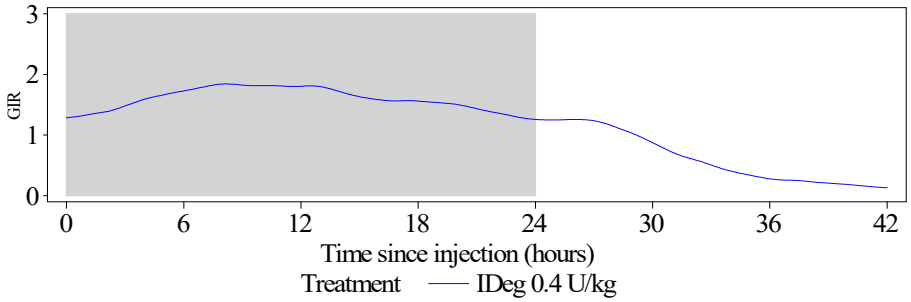


Figure 1-1: Mean glucose infusion rate profile (steady state) for Tresiba® at dose of 0.4 U/Kg in patients with Type 1 diabetes mellitus

In patients with type 1 diabetes, the total glucose-lowering effects of Tresiba® over 24 hours increase approximately in proportion to the SC doses between 0.4 U/kg to 0.8 U/kg. At steady-state, within-subject day-to-day variability measured as within subject coefficient of variation (CV) in total glucose lowering effect ($AUC_{GIR,T,SS}$) was 20% with Tresiba®.

The 24-hour total glucose-lowering effect of Tresiba® 100 units/mL and 200 units/mL was comparable after administration of the same dose at 0.4 U/kg in a euglycemic clamp study following 8 days of once-daily injection.

10.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after the first of 8 once-daily subcutaneous of Tresiba® at 0.4 U/kg, onset of appearance of serum insulin degludec was around one hour and the mean maximum concentration of 2076 pmol/L occurred between 11-13 hours. Steady state serum concentration is reached after 3-4 days of once daily Tresiba® subcutaneous administration. Following the last dose at steady state, maximum insulin degludec concentrations of 4472 pmol/L were attained at a median of 9 hours. At dose range of 0.4 – 0.8U/kg, total exposure and maximum concentration of insulin degludec increased in a dose proportional manner after subcutaneous administration. The insulin degludec exposure at steady-state is comparable between Tresiba® 100 units/mL and 200 units/mL when the same U/kg dose was administered.

Distribution:

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. The results of the in vitro protein binding studies demonstrate that there is no clinically relevant interaction between insulin degludec and other protein bound drugs.

Elimination

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life is approximately 25 hours independent of dose.

Degradation of Tresiba® is similar to that of human insulin; all metabolites formed are inactive.

Special Populations and Conditions

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

- **Pediatrics** Pharmacokinetic properties of Tresiba® were investigated in 12 children (≥6 to 11 years), 13 adolescents (12 to 17 years), and 12 adults (18 to ≤65 years). In this study, total exposure of Tresiba® after a single dose was, higher in children and adolescents than in adults with type 1 diabetes mellitus. Using data from this study, as well as sparse sampling of steady-state serum concentration data from 169 pediatric subjects (1 to 17 years) with type 1 diabetes from Trial 3561 (see 14 CLINICAL TRIALS), population pharmacokinetic analysis was conducted for Tresiba®. When dosed per kg body weight, model-derived concentration-time profiles of Tresiba® in children and adolescents were, at steady-state, comparable to those observed in adults with type 1 diabetes mellitus.

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

- **Sex** The effect of gender on the pharmacokinetics of Tresiba® was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic trials. Overall, there was no difference in the pharmacokinetic properties of insulin degludec between female and male subjects.

- **Pregnancy and Breast-feeding** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of Tresiba® has not been studied (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnancy). A clinical trial in pregnant women investigated the efficacy and safety of Tresiba® compared to insulin detemir (see 14 CLINICAL TRIALS); approximately two-thirds of infants exposed to Tresiba® during gestation had quantifiable levels of insulin degludec in their cord blood at birth. No study of the use of Tresiba during breastfeeding has been conducted.

- **Ethnic Origin** Tresiba® has been studied in a pharmacokinetic and pharmacodynamic trial in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

- **Hepatic Insufficiency** Tresiba® has been studied in a pharmacokinetic trial in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single dose (0.4U/kg) of Tresiba®. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No differences in the pharmacokinetics of Tresiba® were identified between healthy subjects and subjects with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS).
- **Renal Insufficiency** Tresiba® pharmacokinetics was studied in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 U/kg) of Tresiba®. Renal function was defined using creatinine clearance (Clcr) as follows: ≥ 90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and < 30 mL/min (severe).
- Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total (AUCIDeg,0-120h,SD) and peak exposure of Tresiba® were on average about 10-25% and 13-27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of Tresiba® (CL/FIDeg,SD) in subjects with ESRD (see 7 WARNINGS AND PRECAUTIONS).

- **Obesity** When corrected for body weight, there is no significant relationship for subjects with T1DM between exposure of Tresiba® and BMI when dosed per kg body weight. For subjects with T2DM, exposure increases and glucose-lowering effect decrease with increasing BMI.

Detailed Pharmacology

Efficacy Pharmacology: In vitro pharmacology studies have been conducted to characterize the molecular biological properties and efficacy of insulin degludec; these included receptor binding and signaling studies as well as a number of functional cellular assays of insulin action on metabolism in fat, liver and muscle cells. Furthermore, insulin degludec's mitogenic potential has been evaluated in four different cell types. The in vivo pharmacological efficacy of insulin degludec has been determined in both normal rats and insulin-resistant rats. In addition, proof of the prolonged action of insulin degludec has been obtained from studies conducted in pigs.

In Vitro Studies: The in vitro pharmacological studies of insulin degludec have addressed both the mechanism of action and the efficacy in comparison to human insulin. Through receptor-binding assays, it has been demonstrated that the biological effects of insulin degludec are mediated by specific binding to the insulin receptor in all species tested (rat, dog, rabbit, pig and human), and subsequent activation of insulin receptor tyrosine phosphorylation and further

downstream intra-cellular signaling pathway. Thus the mode of action of this modified insulin analogue is identical to that of human insulin and other insulin analogues. Furthermore, a number of functional assays in cells from the major target organs of insulin (fat, liver and muscle) have been conducted, demonstrating that insulin degludec activates the same pattern of metabolic effects as human insulin, including glucose uptake, lipogenesis and the inhibition of lipolysis in fat cells, as well as the stimulation of glycogen synthesis in hepatocytes and muscle cells. In all the cell types examined, insulin degludec was found to demonstrate full efficacy (i.e., is a full insulin receptor agonist).

From a safety perspective, it has been shown that insulin degludec binds to rat, dog and human insulin-like growth factor 1 (IGF-1) receptor with lower affinities relative to human insulin and the ratio between the affinities for binding to the IGF-1 receptor and insulin receptor has been determined to be lower for insulin degludec than for human insulin. In addition, the binding kinetics of insulin degludec for the human insulin receptor and the rate of signal decline are similar to that of human insulin. The mitogenic potency of insulin degludec is lower than that of human insulin when tested in human colon adenocarcinoma cells (COLO-205), primary human mammary epithelial cells (HMEC), L6 rat myoblasts overexpressing the human insulin receptor (L6-hIR) and human mammary adenocarcinoma cells (MCF-7), reflecting the lower insulin receptor binding affinity compared to human insulin. The overall mitogenic/metabolic potency ratio is similar to human insulin, suggesting that the balance between the metabolic and proliferative actions is similar to that of human insulin.

In Vivo Studies: The in vivo pharmacological efficacy of insulin degludec has been determined both in normal rats and insulin-resistant rats. In euglycemic-hyperinsulinemic clamp studies conducted in rats and pigs insulin degludec maintains the pharmacological actions of human insulin as demonstrated by its blood glucose–lowering effect.

Safety Pharmacology: Insulin degludec has been investigated in a series of safety pharmacology studies assessing its effects on cardiovascular and respiratory function, and the central nervous system in pharmacological responsive animals (rat and dog). Special in vitro cardiovascular studies were also performed. The highest dose tested was 50 U/kg in rat and 4 U/kg in dog. Overall, insulin degludec was well tolerated in the safety pharmacology program and no findings were observed, except those associated with hypoglycemia observed at the highest doses.

In conclusion, the safety pharmacology program raised no safety concerns.

11 STORAGE, STABILITY AND DISPOSAL

Before first use:

Store in a refrigerator (2°C – 8°C). Keep away from the freezing element. Do not freeze.

FlexTouch®: Keep the cap on the pen in order to protect from light.

After first opening or carried as a spare:

FlexTouch®: Can be stored at room temperature (not above 30°C) or in a refrigerator (2°C –

8°C) for up to 8 weeks. Keep the cap on the pen in order to protect from light.

Penfill®: Do not refrigerate. Can be stored at room temperature (not above 30°C) for up to 8 weeks. Keep the cartridges in the outer carton in order to protect from light.

The storage conditions are summarized in Table 1-6.

Table 1-6: Storage Conditions for Tresiba® FlexTouch® and Penfill® cartridge

	Not in-use (unopened) **Refrigerated (2°C – 8°C)**	**Not in-use (unopened)** **Room Temperature (below 30°C)**	**In-use (opened)** **Refrigerated (2°C - 8°C)**	**In-use (opened)** **Room Temperature (below 30°C)**
3 mL Tresiba® 100 U/mL PenFill®	Until expiration date	56 days (8 weeks) Do not refrigerate	Do not refrigerate product in-use.	56 days (8 weeks) Do not refrigerate
3 mL Tresiba® 100 U/mL and 200 U/mL FlexTouch®	Until expiration date	56 days (8 weeks) Do not refrigerate	56 days (8 weeks)	56 days (8 weeks)

Penfill®: The cartridges are designed to be used with Novo Nordisk delivery systems (durable devices for repeated use) and NovoFine® and/or NovoFine® Plus needles. Detailed instruction accompanying the delivery system must be followed.

FlexTouch®: An easy-to-use prefilled insulin pen with a light-touch button that is specifically designed to be used with NovoFine® and/or NovoFine® Plus needles

12 SPECIAL HANDLING INSTRUCTIONS

Penfill® and/or FlexTouch® and needles must not be shared. The cartridge must not be refilled. Tresiba® must not be used if it does not appear clear and colourless. Tresiba® which has been frozen must not be used. The patient should be advised to discard the needle after each injection.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: insulin degludec injection

Chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin

Molecular formula and molecular mass: C274H411N65O81S6 and 6103.97

Structural formula:

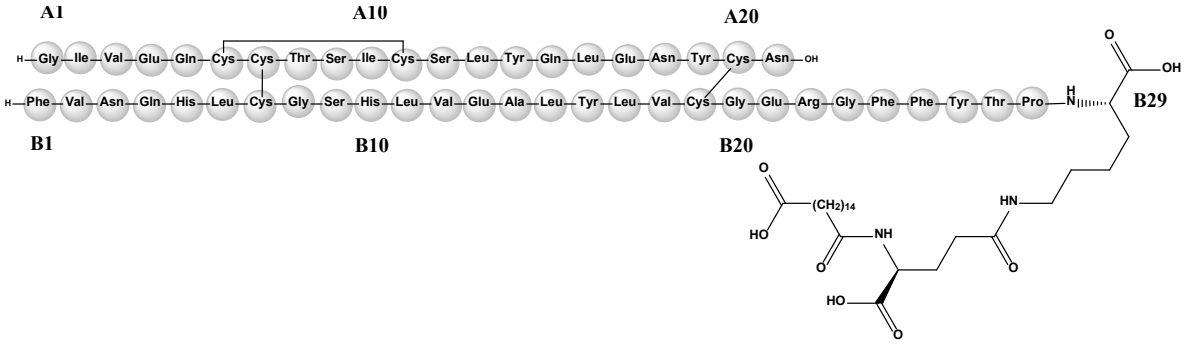


Figure 2-1: Structural formula of insulin degludec

Physicochemical properties: 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.

Product Characteristics:

Tresiba® is a sterile, aqueous, clear, and colourless solution that contains insulin degludec 100 Units/mL (U-100) or 200 Units/mL (U-200).

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

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

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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Type 1 Diabetes Mellitus

The efficacy of Tresiba® administered once-daily either at the same time each day or at any time each day in adult patients with type 1 diabetes and used in combination with a mealtime insulin was evaluated in three randomized, phase 3a, open-label, treat-to-target, active-controlled, trials. Across these trials (n= 1577), the mean age was 43; the mean duration of diabetes was 17.3 years; the mean BMI was 25.8 kg/m^2; 56.3% of patients were male; 80.4% were White; 1.5% were Black or African American; 4.4% were Hispanic; and 7.0% had eGFR<60 mL/min/1.73m^2.

The use of Tresiba® in pediatric patients 2 years of age and older with type 1 diabetes mellitus is supported by evidence from a 26 weeks, multi-centre, multinational, open-label, randomized, two arm parallel, treat-to-target trial.

The efficacy of Tresiba® in women with type 1 diabetes who were between weeks 8 and 13 of gestation or who intend to become pregnant was evaluated in a randomized, phase 3b, open-label, multicentre trial.

Type 2 Diabetes Mellitus

The efficacy of Tresiba® administered once-daily either at the same time each day or at any time each day in adult patients with type 2 diabetes and used in combination with a mealtime insulin or in combination with common oral anti-diabetic agents was evaluated in four randomized, phase 3a, open-label, treat-to-target active-controlled trials. Across these trials n=3166), the mean age was 58; the mean duration of diabetes was 10.7 years; the mean BMI was 31.3 kg/m^2; 56.4% of patients were male; 80.6% were White; 7.8% were Black or African American; 13.1% were Hispanic; and 9.3% had eGFR<60 mL/min/1.73m^2.

The cardiovascular safety of Tresiba® was evaluated in one double-blinded, event-driven trial (DEVOTE) of 2-year median duration in patients with type 2 diabetes at high risk of cardiovascular events (refer to table 2-10).

Table 2-1: Summary of patient demographics for clinical trials in Type 1 Diabetes (Adult and Pediatric)

Study #	Trial design and duration	Dosing and route of administration	Number of study subjects	Mean age (SD) and range	Gender
Trial A **(3583)**	52 Weeks; Multi-centre, multi-national, randomized (3:1), open-label, two-arm, parallel group, treat-to-target trial.	Tresiba® (O.D)*: S.C Insulin glargine (O.D)**: S.C	629 Tresiba®: 472 Insulin glargine 100 U/mL: 157	Mean age: 43.0 (13.6) Range: 18.4; 78.2	M: 368 F: 261

Study #	Trial design and duration	Dosing and route of administration	Number of study subjects	Mean age (SD) and range	Gender
Trial B (3585)	26 Weeks; Multi-centre, multi-national randomized (2:1), open-label, two arm, parallel group, treat to-target trial.	Tresiba® (O.D)*: S.C Insulin detemir (O.D): S.C	455 TRESIBA®: 302 Insulin detemir: 153	Mean age: 41.3 (14.7) Range: 18.1; 80.9	M: 236 F: 219
Trial C (3770)	26 Weeks; Multi-centre, multi-national randomized (1:1:1), three arm, open-label, parallel group, treat-to-target trial.	Tresiba® (dosed at alternating times): S.C Tresiba® (O.D)*: S.C Insulin glargine (O.D)**: S.C	493 Tresiba®: (dosed at alternating times): 164 Tresiba® (O.D): 165 Insulin glargine 100 U/mL: 164	Mean age: 43.7 (13.1) Range: 19.3; 82.4	M: 284 F: 209
Trial D **(3561)**	26 Weeks; Multi-centre, multinational, open label, randomized, two arm parallel group, treat-to-target trial.	Tresiba® (O.D.): S.C. Insulin detemir (O.D. or B.I.D., as required): S.C.	350 Tresiba®: 174 Insulin detemir: 176	Mean age: 10.0 (4.4) Range: 1.5; 18.4+	M: 194 F: 156
EXPECT **(4300)**	25 month (maximum); Multi-centre, randomized (1:1), open label, parallel-group, treat-to-target, active controlled trial.	Tresiba® (O.D): S.C Insulin detemir (O.D or BID): S.C.	188 Tresiba®: 92 Insulin detemir: 96	Mean age: 30.8 (5.15) Range: 18.0; 42.0	M: 0 F: 188

O.D: Once daily; B.I.D.: Twice daily; S.C: Subcutaneous; M: Male; F: Female

* Tresiba® was administered once daily in the evening
** Insulin glargine was administered once daily according to local labelling
+For German subjects (14 in full analysis set), their date of birth was set to January 1st for protection of subject anonymity. For one subject on TRESIBA® OD, this led to a derived age at screening of 18.4 years. In reality, this subject was less than 18 years of age at screening.

Table 2-2: Summary of patient demographics for clinical trials in Type 2 Diabetes (Adult)

Study #	Trial design and duration	Dosing and route of administration	Number of study subjects	Mean age (SD) and range	Gender
Trial E (3579)	52 Weeks; Multi-centre, multi-national randomized (3:1), three arm, open-label, parallel group, treat-to-target trial	Tresiba® (O.D)*: S.C Insulin glargine (O.D)**: S.C	1030 Tresiba®: 773 Insulin glargine 100 U/mL: 257	Mean age: 59.1 (9.8) Range: 21.9; 87.0	M: 638 F: 392
Trial F (3672)	26 Weeks; Multi-centre, multi-national randomized (1:1), open-label, parallel group, treat-to-target trial.	Tresiba® 200 U/mL(O.D)*: S.C Insulin glargine (O.D)**: S.C	457 Tresiba®: 228 Insulin glargine 100 U/mL: 229	Mean age: 57.5 (9.2) Range: 31.0; 78.0	M: 243 F: 214
Trial G (3668)	26 Weeks; Multi-centre, multi-national randomized (1:1:1), open-label, three arm, treat-to-target trial.	Tresiba® (dosed at alternating times)): S.C TRESIBA® (O.D)*:S.C Insulin glargine (O.D)**: S.C	687 Tresiba® (dosed at alternating times): 229 Tresiba® (O.D): 228 Insulin glargine 100 U/mL: 230	Mean age: 56.4 (9.6) Range: 22.9; 80.9	M: 370 F: 317
Trial H (3582)	52 Weeks; Multi-centre, multi-national randomized (3:1), open-label, two-arm, parallel group, treat-to-target trial.	Tresiba® (O.D)*: S.C Insulin glargine (O.D)**: S.C	992 TRESIBA®: 744 Insulin glargine 100 U/mL: 248	Mean age: 58.9 (9.3) Range: 23.1; 86.3	M: 538 F: 454
DEVOTE (4080)	Multi-centre, multi-national, randomized, double-blinded, active-controlled, treat-to-target, event-driven trial for a median duration of 2 years.	Tresiba® (O.D)*: S.C insulin glargine (O.D)**: S.C Both with standard of care	7637 Tresiba®: 3818 insulin glargine 100 U/mL: 3819	Mean age: 65 (7.4) Range: 46.0 ; 93.0	M: 4778 F: 2859

O.D: Once daily; S.C: Subcutaneous; M: Male; F: Female
* Tresiba® was administered once daily in the evening
** Insulin glargine was administered once daily according to local labelling

14.2 Study Results

Type 1 Diabetes – Adult

Tresiba® Administered at the Same Time each Day in Combination with a Rapid-Acting Insulin Analogue at Mealtimes

Trial A
The efficacy of Tresiba® was evaluated in a 52-week randomized, open-label, multicenter trial in 629 patients with type 1 diabetes mellitus (Trial A). Patients were randomized to Tresiba® once-daily with the evening meal, or insulin glargine 100 U/mL once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms.The primary objective of the study was to demonstrate the non-inferiority of Tresiba® compared to insulin glargine 100 U/mL in change in HbA_{1c} from baseline at 52 weeks, with a non-inferiority margin of 0.4%.

At week 52, treatment with Tresiba® was non-inferior to insulin glargine 100 U/mL (Table 2-3, Trial A) in change in HbA_{1c} from baseline.

Trial B
The efficacy of Tresiba® was evaluated in a 26-week randomized, open-label, multicenter trial in 455 patients with type 1 diabetes mellitus (Trial B). Patients were randomized to Tresiba® or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed twice-daily. At end of trial, 67.1% used insulin detemir once daily and 32.9% used insulin detemir twice daily. Insulin aspart was administered before each meal in both treatment arms. The primary objective of the study was to demonstrate the non-inferiority of Tresiba® compared to insulin detemir in change in HbA_{1c} from baseline at 26 weeks, with a non-inferiority margin of 0.4%.

At week 26, treatment with Tresiba® was non-inferior to insulin detemir (Table 2-3, Trial B) in change in HbA_{1c} from baseline.

Table 2-3: Results at Week 52 in a Trial Comparing Tresiba® to Insulin glargine 100 U/mL (Trial A) and Week 26 in a Trial Comparing Tresiba® to Insulin detemir (Trial B) in Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at Mealtimes

	Trial A		**Trial B**	
	Tresiba® + Insulin aspart	Insulin glargine 100 U/mL + Insulin aspart	**Tresiba®** + Insulin aspart	Insulin detemir + Insulin aspart
N	472	157	302	153
HbA_{1c} (%)				
Baseline	7.7	7.7	8.0	8.0
End of trial*	7.3	7.4	7.3	7.4
Adjusted Mean change from baseline	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference [95% CI] TRESIBA® - basal insulin 100 U/mL	-0.01 [-0.14; 0.11]		-0.09 [-0.23; 0.05]	

	Trial A		Trial B	
	Tresiba® + Insulin aspart	Insulin glargine 100 U/mL + Insulin aspart	**Tresiba®** + Insulin aspart	Insulin detemir + Insulin aspart
Proportion achieving HbA_{1c} < 7% at trial end	39.8%	42.7%	41.1%	37.3%
FPG (mmol/L)				
Baseline	9.1	9.7	9.9	9.5
End of trial*	7.7	8.1	7.4	9.0
Adjusted mean change from baseline	-1.53	-1.20	-2.40	-0.75
Daily basal insulin dose				
Baseline mean	28 U	26 U	22 U	22 U
Mean dose at end of trial	29 U[1]	32 U[1]	25 U[2]	29 U[2]
Daily bolus insulin dose				
Baseline mean	29 U	29 U	28 U	30 U
Mean dose at end of trial	33 U[1]	35 U[1]	36 U[2]	42 U[2]

*LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; FPG = fasting plasma glucose
[1] At Week 52
[2] At Week 26
Change from baseline in HbA_{1c} after 26 weeks (trial A) and 52 weeks (trial B) of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). In trial A, there were15% of subjects on insulin degludec and 12 % of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 52 weeks. In trial B, there were 6% of subjects on insulin degludec and 10 % of subjects on insulin detemir for whom HbA1c measurements were missing at 26 weeks.

Trial C

Tresiba® Administered at the Same Time each Day or at Any Time each Day in Combination with a Rapid-Acting Insulin Analogue at Mealtimes

The efficacy of Tresiba® was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to Tresiba® injected once-daily at the same time each day (with the main evening meal), to Tresiba® injected once daily at any time each day or to insulin glargine 100 U/mL injected once-daily according to the approved labeling. The any time each day Tresiba® arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). Tresiba® in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Insulin aspart was administered before each meal in both treatment arms. The primary objective of the study was to demonstrate the non-inferiority of Tresiba® injected at alternating times compared to insulin glargine 100 U/mL in change in HbA_{1c} from baseline at 26 weeks, with a non-inferiority margin of 0.4%.

At week 26, treatment with Tresiba® injected at alternating times was non-inferior to insulin glargine 100 U/mL (Table 2-4) in change in HbA_{1c} from baseline.

Table 2-4: Results at Week 26 in a Trial Comparing Tresiba® Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin glargine 100 U/mL in Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at mealtimes

	Tresiba® at the same time each day + Insulin aspart	**Tresiba®** at alternating times + Insulin aspart	Insulin glargine 100 U/mL + Insulin aspart
N	165	164	164
HbA_{1c} (%)			
Baseline	7.7	7.7	7.7
End of trial*	7.3	7.3	7.1
Adjusted mean change from baseline*	-0.41	-0.40	-0.57
Estimated treatment difference [95% CI] Tresiba® alternating - insulin glargine 100 U/mL		0.17 [0.04;0.30]	
Proportion Achieving HbA_{1c} < 7% at Trial End	37.0%	37.2%	40.9%
FPG (mmol/L)			
Baseline	10.0	9.6	9.7
End of trial*	7.4	8.4	8.4
Adjusted mean change from baseline	-2.32	-1.37	-1.33
Daily basal insulin dose			
Baseline mean	28 U	29 U	29 U
Mean dose at end of study	33 U	35 U	35 U
Daily bolus insulin dose			
Baseline mean	29 U	33 U	32 U
Mean dose at end of study	27 U	29 U	35 U

*LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; FPG = fasting plasma glucose
Change from baseline in HbA_{1c} after 26 weeks of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). There were16% of subjects on insulin degludec (dosed at same time), 16 % of subjects on insulin degludec (dosed alternatively) and 8% of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 26 weeks.

Type 1 Diabetes – Pediatric

Trial D
Tresiba® Administered at the Same Time each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Pediatric Patients Between 1 to less than18 years of Age

The efficacy of Tresiba® was evaluated in a 26 week randomized, open label, multicenter trial in 350 pediatric patients with type 1 diabetes mellitus.

Patients were randomized to Tresiba® once-daily or insulin detemir once or twice-daily. Randomization was stratified according to age group (1 to <6; 6 to < 12; and 12 to < 18 of age). 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 the end of the trial, 37.7% used insulin detemir once daily and 62.3% used insulin detemir twice daily.

Patients in the Tresiba® arm included 43 children aged 1-5 years, 70 children aged 6-11 years and 61 adolescents aged 12-17 years. The mean duration of diabetes was 4 years. 55.4% were male. 74.6% were White, 2.9% Black or African American. 2.9% were Hispanic. The mean BMI was 18.6 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between Tresiba® and insulin detemir was 0.15% with a 95% confidence interval of [-0.03%; 0.33%] and met the pre-specified non-inferiority margin (0.4%) (see Table 2-5).

Table 2-5: Results at Week 26 in a Trial Comparing Tresiba® to Insulin detemir in Pediatric Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	Tresiba® + Insulin aspart	Insulin detemir + Insulin aspart
N	174	176
HbA_{1c} (%)		
Baseline	8.2	8.0
End of 26 weeks	8.0	7.7
Adjusted mean change from baseline after 26 weeks*	-0.19	-0.34
Estimated treatment difference [95%CI] TRESIBA® v. Insulin detemir	0.15 [-0.03, 0.33]	
FPG (mmol/L)		
Baseline	9.0	8.4
End of 26 weeks**	11.57	11.99
Adjusted mean change from baseline after 26 weeks	2.89	3.31
Daily basal insulin dose		
Baseline mean	15 U (0.37 U/kg)	16 U (0.41 U/kg)
Mean dose after 26 weeks	16 U (0.37 U/kg)	21 U (0.51 U/kg)
Daily bolus insulin dose		
Baseline mean	20 U (0.50 U/kg)	20 U (0.52 U/kg)
Mean dose after 26 weeks	23 U (0.56 U/kg)	22 U (0.57 U/kg)

*The change from baseline to end of treatment visit in HbA_{1c} was analyzed using ANOVA with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate. There were 2.9% of subjects in TRESIBA® and 6.3% insulin detemir arms for whom data was missing at the 26-week HbA_{1c} measurement and missing data was imputed by multiple imputation carrying forward the baseline value and adding an error term.
**LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; FPG = fasting plasma glucose

Type 2 Diabetes – Adult

Trial E

Tresiba® Administered at the Same Time each Day as an Add-on to Metformin with or without a DPP-4 inhibitor in Insulin Naïve Patients

The efficacy of Tresiba® was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA® once-daily with the evening meal or insulin glargine 100 U/mL 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 primary objective of the study was to

demonstrate the non-inferiority of Tresiba®compared to insulin glargine 100 U/mL, both added on to metformin with or without a DPP-4 inhibitor, in change in HbA_{1c} from baseline at 52 weeks, with a non-inferiority margin of 0.4%.

At week 52, treatment with Tresiba® was non-inferior to insulin glargine 100 U/mL (Table 2-6) in change in HbA_{1c} from baseline.

Table 2-6: Results at Week 52 in a Trial Comparing Tresiba® to Insulin glargine 100 U/mL in Patients with Type 2 Diabetes Mellitus on OAD(s)**

	Tresiba® + met ± DPP-4 inhibitor	Insulin glargine 100 U/mL + met ± DPP-4 inhibitor
N	773	257
HbA_{1c} (%)		
Baseline	8.2	8.2
End of trial*	7.1	7.0
Adjusted mean change from baseline	-1.06	-1.15
Estimated treatment difference [95% CI] TRESIBA® - insulin glargine 100 U/mL	0.09 [-0.04; 0.22]	
Proportion achieving HbA_{1c} < 7% at trial end	51.7%	54.1%
FPG (mmol/L)		
Baseline	9.6	9.7
End of trial*	5.9	6.3
Adjusted mean change from baseline	-3.77	-3.34
Daily insulin dose		
Baseline mean (starting dose)	10 U	10 U
Mean dose after 52 weeks	59 U	60 U

*LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; met = metformin; FPG = fasting plasma glucose; ** OAD: oral antidiabetic agent;
Change from baseline in HbA_{1c} after 52 weeks of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). There were 21% of subjects on insulin degludec and 22% of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 52 weeks.

Trial F

Tresiba® U-200 Administered at the Same Time each Day as an Add-on to Metformin with or without a DPP-4 inhibitor in Insulin Naïve Patients

The efficacy of Tresiba® 200 U/mL 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® 200 U/mL once-daily with the evening meal or insulin glargine 100 U/mL 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 primary objective of the study was to demonstrate the non-inferiority of Tresiba® compared to insulin glargine 100 U/mL, both added on to metformin with or without a DPP-4 inhibitor, in change in HbA_{1c} from baseline at 26 weeks, with a non-inferiority margin of 0.4%.

At week 26, treatment with Tresiba® was non-inferior to insulin glargine 100 U/mL (Table 2-7) in change in HbA_{1c} from baseline.

Table 2-7: Results at Week 26 in a Trial Comparing Tresiba® 200 U/mL to Insulin glargine 100 U/mL in Patients with Type 2 Diabetes Mellitus on OAD(s)**

	Tresiba® 200 U/mL + met ± DPP-4	Insulin glargine 100 U/mL + met ± DPP-4
N	228	229
HbA_{1c} (%)		
Baseline	8.3	8.2
End of trial*	7.1	7.1
Adjusted mean change from baseline	-1.18	-1.22
Estimated treatment difference [95% CI] TRESIBA® - insulin glargine 100 U/mL	0.04 [-0.11; 0.19]	
Proportion achieving HbA_{1c} < 7% at trial end	52.2%	55.9%
FPG (mmol/L)		
Baseline	9.6	9.7
End of trial*	5.7	6.1
Adjusted mean change from baseline	-3.94	-3.52
Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	62 U	63 U

*LS mean values from the statistical analysis

Abbreviation: HbA_{1c} = hemoglobin A1c; met = metformin; FPG = fasting plasma glucose;**OAD: Oral antidiabetic agent

Change from baseline in HbA_{1c} after 26 weeks of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). There were 12% of subjects on insulin degludec and 13% of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 26 weeks.

Trial G

Tresiba® Administered at the Same Time each Day or Any Time each Day as an Add-on to One and up to Three of the Following Oral Agents: Metformin, Sulfonylurea or Glinides or Pioglitazone

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. Basal insulin alone was taken by 3.1% of patients, 57.9% were treated with OAD(s) alone and 38.7% were treated with basal insulin and OAD(s). 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 100 U/mL 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 continued as background therapy in both treatment arms, in subjects who were treated with these OADs prior to entering the trial. The primary objective of the study was to demonstrate the non-inferiority of Tresiba® compared to insulin glargine 100 U/mL, both added

on to OAD(s) as applicable, in change in HbA_{1c} from baseline at 26 weeks, with a non-inferiority margin of 0.4%.

At week 26, treatment with Tresiba® was non-inferior to insulin glargine 100 U/mL (Table 2-8) in change in HbA_{1c} from baseline.

Table 2-8: Results at Week 26 in a Trial Comparing Tresiba® at same and alternating times to Insulin glargine 100 U/mL in Patients with Type 2 Diabetes Mellitus on OAD(s)**

	Tresiba® at the same time each day ± OAD(s)*	**Tresiba®** at alternating times ± OAD(s)*	Insulin glargine 100 U/mL ± OAD(s)*
N	228	229	230
HbA_{1c} (%)			
Baseline	8.4	8.5	8.4
End of trial*	7.4	7.3	7.2
Adjusted mean change from baseline	-1.03	-1.17	-1.21
Estimated treatment difference [95% CI] TRESIBA® alternating – insulin glargine 100 U/mL		0.04 [-0.12; 0.20]	
Proportion achieving HbA_{1c} < 7% at trial end	40.8%	38.9%	43.9%
FPG (mmol/L)			
Baseline	8.8	9.0	9.0
End of trial*	5.9	5.9	6.3
Adjusted mean change from baseline	-3.01	-3.05	-2.64
Daily insulin dose			
Baseline mean	21 U	19 U	19 U
Mean dose after 26 weeks	47 U	49 U	47 U

*LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; FPG = fasting plasma glucose; OAD: oral antidiabetic agent
*OAD(s): up to three of the following oral antidiabetic agents (metformin, sulfonylureas, glinides or thiazolidinediones) were continued as background therapy in subjects who had been treated with these OADs prior to entering the trial.
Change from baseline in HbA_{1c} after 26 weeks of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). There were 11% of subjects on insulin degludec (dosed alternatively) and 12% of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 26 weeks.

Trial H

Tresiba® Administered at the Same Time each Day in Combination with a Rapid-Acting Insulin Analogue at Mealtimes

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 any insulin regimen (premix insulin, bolus insulin alone, basal insulin alone or any combination thereof) ± oral antidiabetic agents (OADs). Basal-bolus insulin treatment ± OADs was taken by 49% of patients, 24.4% were treated premix insulin ± OADs and 21.2% were treated with basal insulin ± OADs. Patients were randomized to Tresiba® once-daily with the main evening meal or insulin glargine 100 U/mL 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 and pioglitazone) were continued as background therapy in both treatment arms in subjects who were treated with these OADs prior to entering the trial. The primary objective of the study was to demonstrate the non-inferiority of Tresiba® compared to insulin glargine 100 U/mL, both added on to mealtime insulin aspart and, as applicable, to metformin and/or pioglitazone, in change in HbA_{1c} from baseline at 26 weeks, with a non-inferiority margin of 0.4%

At week 52, treatment with Tresiba® was non-inferior to insulin glargine 100 U/mL (Table 2-9) in change in HbA_{1c} from baseline.

Table 2-9: Results at Week 52 in a Trial Comparing Tresiba® to Insulin glargine 100 U/mL in Patients with Type 2 Diabetes Mellitus receiving Insulin aspart at mealtimes and OADs**

	Tresiba® + Insulin aspart ± met ± pio	Insulin glargine 100 U/mL + Insulin aspart ± met ± pio
N	**744**	**248**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.2	7.1
Adjusted mean change from baseline	-1.10	-1.18
Estimated treatment difference [95% CI] TRESIBA® - insulin glargine 100 U/mL	0.08 [-0.05; 0.21]	
Proportion achieving HbA_{1c} < 7% at trial end	49.5%	50.0%
FPG (mmol/L)		
Baseline	9.2	9.2
End of trial*	7.0	7.2
Adjusted mean change from baseline	-2.25	-1.96
Daily basal insulin dose		
Baseline mean	42 U	41 U
Mean dose after 52 weeks	72 U	66 U
Daily bolus insulin dose		
Baseline mean	33 U	33 U
Mean dose after 52 weeks	70 U	72 U

*LS mean values from the statistical analysis
Abbreviation: HbA_{1c} = hemoglobin A1c; FPG = fasting plasma glucose; OAD: oral antidiabetic agent; met = metformin; pio = pioglitazone
**OAD: oral antidiabetic agent
Change from baseline in HbA_{1c} after 52 weeks of treatment is analysed using an ANOVA method with treatment, region, sex and antidiabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. Missing data is imputed using last observation carried forward (LOCF). There were 16% of subjects on insulin degludec and 15% of subjects on insulin glargine for whom HbA_{1c} measurements were missing at 52 weeks.

Cardiovascular Outcomes Trial

DEVOTE was a multi-center, multi-national, randomized, double-blinded, active-controlled, treat-to-target, event-driven non inferiority 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 for diabetes and cardiovascular disease for a median duration of 2 years.

Patients eligible to enter the trial were; 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA

class II and III heart failure (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

At baseline, demographic and disease characteristics were balanced between treatment groups. The mean age of the trial population was 65 years and the mean duration of diabetes was 16.4 years. The population was 62.6% male, 75.6% White 10.9% Black or African American, 10.2% Asian. 14.9% had Hispanic ethnicity. The mean HbA_{1c} was 8.4% and the mean BMI was 33.6 kg/m^2. The baseline mean estimated glomerular filtration rate (eGFR) was 68 mL/min/1.73m^2. 41% of patients had eGFR 60-90 mL/min/1.73m^2; 35% of patients had eGFR 30 to 60 mL/min/1.73 m^2 and 3% of patients had eGFR <30 mL/min/1.73 m^2. Previous history of severe hypoglycemia 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.

The primary endpoint was time from randomization to first occurrence of an Event Adjudication Committee (EAC)-confirmed 3- component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Non-inferiority of Tresiba® to Insulin Glargine was considered confirmed if the upper limit of the two-sided 95% confidence interval for the hazard ration (HR) of MACE was below 1.3.

The time to first occurrence of MACE with Tresiba® as compared to insulin glargine U-100 was non-inferior (HR: 0.91; 95% CI [0.78 ;1.06]; see Figure 2-3). The results of the primary composite MACE endpoint and a summary of its components are shown in Table 2-10.

Table 2-10: Analysis of the Composite 3-point MACE and Individual Cardiovascular Endpoints in DEVOTE

	Tresiba®		**Insulin glargine U-100**		
N	**3818**		**3819**		
	Number of Patients (%)	**Rate per 100 PYO***	**Number of Patients (%)**	**Rate per 100 PYO***	**Hazard Ratio# (95% CI)**
Composite of first event of CV death, non-fatal MI, or non-fatal stroke (3-Point MACE)	325 (8.5)	4.41	356 (9.3)	4.86	0.91 [0.78; 1.06]
CV death	136 (3.6)	1.80	142 (3.7)	1.88	
Non-fatal MI	144 (3.8)	1.94	169 (4.4)	2.28	
Non-fatal stroke	71 (1.9)	0.95	79 (2.1)	1.06	

* PYO = patient-years of observation until first MACE, death, or trial discontinuation
# Hazard rate-ratio and 95% CI is based on a cox proportional hazards regression.

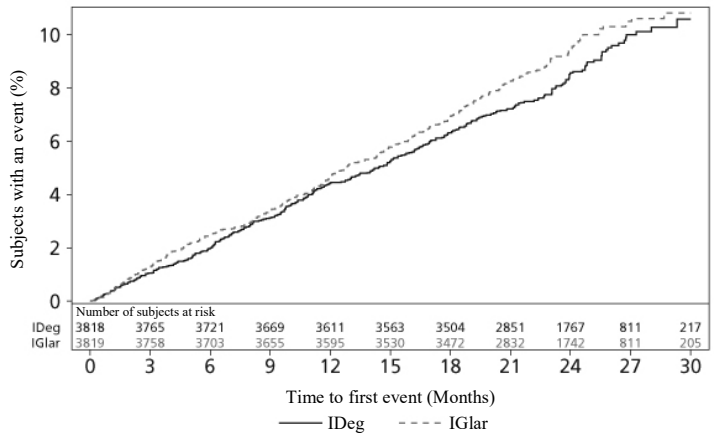


Figure 2-3: Cumulative Event Probability for Time to First EAC-Confirmed MACE in DEVOTE

Confirmatory secondary endpoints included the number of EAC-confirmed severe hypoglycemic episodes, and the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a subject (yes/no). Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not have been available during an event, but 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. Results for the confirmatory secondary endpoints are shown in Table 2-11.

Table 2-11: Severe Hypoglycemic Episodes in Patients Treated with TRESIBA® or Insulin Glargine U-100 in DEVOTE

	TRESIBA®[1]	**Insulin glargine** (100 units/mL)[1]
N	**3,818**	**3,819**
Rate of severe hypoglycemia (per 100 patient years of observation)		
	3.70	6.25
	Rate ratio: 0.60 [0.48; 0.76]#*	
Proportions of patients with severe hypoglycemia (percent of patients)		
	4.9%	6.6%
	*Odds ratio**: 0.73 [0.60; 0.89]#*	

1 In addition to standard of care for diabetes and cardiovascular disease
* The rate ratio and 95% CI is based on a negative-binomial regression with log (PYO) as an offset.
** The odds-ratio and 95% CI is based on a logistic regression.
# Test for superiority evaluated at 5% level for significant, (2-sided p<0.001). The Type I error was controlled by means of a pre-specified hierarchical testing strategy.

EXPECT (4300) - Pregnancy Trial

The efficacy of Tresiba® has been studied in an open-label, randomised, active controlled clinical trial, in which pregnant women with type 1 diabetes mellitus were treated within a basal-bolus treatment regimen with Tresiba® or insulin detemir as basal insulin, both in combination

with insulin aspart as mealtime insulin. Mean duration of exposure during pregnancy was 182.5 days for Tresiba® (range 7-266 days) and 175 days for insulin detemir (range 11-270 days).

The mean age was 31.2 years, with 96.0% subjects between 18 to 40 years of age. The mean duration of diabetes was 14.4 years, 95.1% were white, 0.4% were Black or African American and 16.9% were Hispanic. The mean BMI was approximately 25.3 kg/m^2.

Tresiba® was non-inferior to insulin detemir as measured by HbA_{1c} at last planned HbA_{1c} visit prior to delivery after GW 16. No difference between treatment groups was observed for glycemic control (change in HbA_{1c}, FPG and PPG) during pregnancy. At the last planned visit prior to delivery, the difference in HbA_{1c} reduction from baseline between Tresiba® and insulin detemir was -0.11% with a 95% confidence interval of [-0.31%; 0.08%] and met the pre-specified non-inferiority margin (0.4%). At baseline, mean HbA1c was 6.73% for Tresiba® and 6.56% for insulin detemir and at gestational week 36 mean HbA1c was 6.30% for Tresiba® and 6.26% for insulin determir.

FPG was numerically lower for subjects treated with Tresiba® at last planned visit prior to delivery (6.17 mmol/L Tresiba®, 6.79 mmol/L insulin detemir).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Single Dose Toxicity
Single subcutaneous administration of insulin degludec in rats (4000 U/kg body weight) and dogs (5 U /kg body weight) was well-tolerated without mortality.

Repeated Dose Toxicity
Repeat-dose toxicity studies with subcutaneous administration of insulin degludec (4- and 26-week studies) in the rat and the dog did not reveal any safety concerns for short-term or chronic use in humans. The no-observed-adverse-effect-level was 10 U/kg body weight/day in rat and 1.3 U/kg/day in the dog. Dosing of insulin degludec to healthy normo-glycemic animals lowered blood glucose to levels below the normal physiological concentration and thereby induced clinical signs of hypoglycemia and hypoglycemia-related mortality. These effects were dose-limiting factors in both species tested. In addition, the effect on blood glucose resulted in compensatory adaptive changes such as increased body weight gain, increased food consumption, various changes in clinical pathology, decreased liver weight and depletion of liver glycogen. The changes seen were similar in nature and magnitude to those induced by NPH insulin and were accordingly considered related to the pharmacological effects of insulin.

Carcinogenesis and Mutagenesis
In a 52-week carcinogenicity study rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 U/kg/body weight/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 U/kg/day; human insulin was dosed at 6.7 IU/kg/day as a comparator. No compound-related increases in incidences of hyperplasia or in benign or malignant tumors were recorded in female mammary glands from rats and no compound related changes in the female mammary gland cell proliferation were observed.

Overall, no compound-related changes in the occurrence of hyperplastic or neoplastic lesions were seen in any animals dosed with insulin degludec compared to vehicle or human insulin exposed animals.

Insulin degludec consists of desB30 human insulin, glutamate and 1,16-hexadecanedioic acid. None of the individual components possess a mutagenic potential, and genotoxicity studies were not performed.

Developmental Toxicity
Female rats were subcutaneously administered insulin degludec and human insulin before mating and throughout pregnancy until weaning, while rabbits were exposed during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin as both resulted in pre- and post-implantation losses and skeletal malformations and variations in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to maternal hypoglycemia, as similar effects are seen after human insulin induced hypoglycemia in non-diabetic animals.

Impairment of Fertility
In a combined fertility and embryo-fetal development study in rats, subcutaneous administration to insulin degludec (up to 21 U/kg/day; approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) had no effect on mating performance or fertility in either males or females.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
TRESIBA®
insulin degludec injection

Read this carefully before you start taking **Tresiba®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Tresiba®**.

Serious Warnings and Precautions

- Low blood sugar (hypoglycemia) is the most common side effect of insulin, including Tresiba®.
- Too low or too high blood sugar can result in the loss of consciousness, coma or death, if untreated.
- Check your blood sugar regularly.
- Do not change your insulin unless instructed by your doctor.
- Do not inject Tresiba® directly into a vein.
- Do not use Tresiba® in insulin infusion pumps.
- Do not use Tresiba® if it does not appear clear and colourless.
- Do not mix Tresiba® with any other insulin.

What is Tresiba® used for?
Tresiba® is a long-acting man-made insulin used to control high blood sugar in adults with diabetes mellitus.
Tresiba® can also be used in children who are 2 years of age and older with type 1 diabetes mellitus.

How does Tresiba® work?
Tresiba® is known as a long-acting insulin analogue.
Tresiba® is similar to the insulin made by your body and helps your body to reduce your blood sugar level. It is used once a day.

What are the ingredients in Tresiba®?
Medicinal ingredients: Insulin degludec
Non-medicinal ingredients: Glycerol, phenol, metacresol, water for injection and zinc acetate

Tresiba® comes in the following dosage forms:

- Tresiba® FlexTouch® 3 mL prefilled pen (100 units/mL)
- Tresiba® FlexTouch® 3 mL prefilled pen (200 units/mL)
- Tresiba® Penfill® 3 mL cartridge (100 units/mL)

Tresiba® FlexTouch® prefilled insulin pens are for use with either NovoFine®, or NovoFine® Plus needles.

Tresiba® Penfill® prefilled insulin cartridges are for use with the Novo Nordisk 3 mL Penfill cartridge compatible delivery devices and either NovoFine® or NovoFine® Plus needles.

Do not use Tresiba® if:

- you are allergic (hypersensitive) to insulin degludec or any of the other ingredients in this medicine.
- you think that your blood sugar is getting too low (this is called “hypoglycemia”).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Tresiba®. Talk about any health conditions or problems you may have, including if you:

- have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- drink alcohol (including wine and beer) your need for insulin may temporarily change as your blood sugar level may either rise or fall.
- have an infection, fever, or have had an operation you may temporarily need more insulin than usual. If you are ill, continue taking your insulin and discuss with your doctor what changes may be right for you.
- suffer from diarrhea, vomiting, or eat less than usual you may temporarily need less insulin than usual.
- exercise more than usual or if you want to change your usual diet.
- are travelling abroad, different time zones may affect your insulin needs and the timing of injections. Discuss with your doctor what changes may be right for you.
- are pregnant, or planning a pregnancy or are breastfeeding, your insulin needs may need to be changed. Careful control of your blood sugar in pregnancy is particularly important for the health of your baby. Discuss with your doctor what changes may be right for you.
- drive, use tools, or operate machinery it is important not to let your blood sugar get too low, because your ability to concentrate and react will be less. Never drive, use tools or operate machinery if you feel like you have low blood sugar.

Other warnings you should know about:

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypoglycemic reactions or if you find it hard to recognize hypoglycemia.

Before you travel, check with your physician or pharmacist on the availability of Tresiba® in other countries. If possible, bring enough Tresiba® with you on your trip.

Thiazolidinediones (a type of diabetes medication that comes in a tablet) can cause localized swelling (edema) and heart failure, especially when taken along with insulin. Tell your doctor straightaway if you have any localized swelling or signs of heart failure such as unusual shortness of breath.
Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder.

When using FlexTouch®, make sure you use the right type of insulin – Always check the insulin

label before each injection. This will help you to avoid accidental mix-ups between different strengths of Tresiba® and between Tresiba® and other insulin products.

When using Penfill®, make sure you use the right type of insulin – Always check the insulin label before each injection. This will help you to avoid accidental mix-ups between Tresiba® and other insulin products.

Do not transfer Tresiba® from the FlexTouch® or Penfill® into a syringe, because the markings on the insulin syringe will not measure the dose correctly and can result in an overdose and severe hypoglycemia.

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted or thickened area. Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Tresiba®:
Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia):
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections)
- Fibrates (medicine used for lowering high levels of blood fats)
- Medicines used to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates
- Sulfonamide antibiotics (medicines used to treat infection)
- Fluoxetine
- Pramlintide
- Somatostatin analogs (such as octreotide)

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia):
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, albuterol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation)
- Medicines used to treat mental health problems, such as: olanzapine, clozapine;
- Hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), somatotropin, thyroid hormones, glucagon;
- Corticosteroids such as cortisone (used to treat inflammation)
- Diuretics (also called water pills), used to treat high blood pressure or fluid retention;
- Isoniazid (used to treat tuberculosis);
- Niacin and phenothiazine
- Protease inhibitors (used to treat HIV infection);

Your blood sugar level may either rise or fall if you take:
- High blood pressure medicines, such as: beta-blockers or clonidine;
- Some medicines used to treat mental health problems, such as: lithium salts;
- Octreotide and lanreotide (used to treat a rare condition involving too much growth hormone (acromegaly))
- Alcohol (including wine and beer)
- A medicine used to treat some parasitic infections, called pentamidine. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Some medicines may make it harder to recognize the warning signs of your blood sugar being too low (hypoglycemia). Such medicines include: beta-blockers medicines, clonidine, guanethidine, or reserpine.

How to take Tresiba®:
Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. Your doctor or Diabetes Educator may provide you with a guide to help track and adjust your dose based on your blood glucose levels. This leaflet is a general guide only. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Before using Tresiba®:
- Check the name on the label to make sure it is Tresiba®.
- Check the strength on the label to make sure you have the correct strength of Tresiba®.
- If using the FlexTouch®, always check that the prefilled pen is not damaged. Do not use it if any damage is seen. Take it back to your supplier or call Novo Nordisk Canada at 1-800-

465-4334 for assistance.

- If using the Penfill®, always check the cartridge, including the rubber stopper (plunger). Do not use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1-800-465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- When using either FlexTouch® or Penfill®, always use a new needle for each injection to prevent contamination. Never reuse a needle.
- Do not share Tresiba® FlexTouch® and Penfill® with another person, even if the needle is changed. Do not reuse or share needles with another person. You may give another person a serious infection or get a serious infection from them.

Do not use Tresiba®:

- In insulin infusion pumps.
- If the FlexTouch® is dropped, damaged or crushed; there is a risk of leakage of insulin.
- If the Penfill® cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge
- is dropped, damaged or crushed; there is a risk of leakage of insulin.
- If the insulin has not been stored correctly or if it has been frozen.
- If the insulin does not appear water-clear and colourless.

Do not refill a Tresiba® Penfill® cartridge.
If you are treated with Tresiba® Penfill® and another insulin in Penfill® cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.
In case of loss or damage, always carry an extra pen and new needles with you in case the insulin delivery device is lost or damaged.

How to inject Tresiba®:

Tresiba® is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle. The best places to inject are the front of your thighs, upper arms or the front of your waist (abdomen). Change the place within the area where you inject each day to reduce the risk of developing lumps and skin pitting.
Use the injection technique advised by your doctor or Diabetes Nurse Educator.

If you are using Tresiba® FlexTouch®, refer to the instructions provided at the end of this leaflet in the section “Instructions on How to Use Tresiba® 100/200 units/mL Solution for Injection in Pre-filled Pen”.

If you are using Tresiba® Penfill®, refer to the instructions provided with your Novo Nordisk Insulin Delivery Device manual.

Usual dose:
Your doctor will decide together with you:

- How much Tresiba® you will need each day.
- When to check your blood sugar level and if you need a higher or lower dose.

- Always follow your doctor's recommendation for dose.
- Use Tresiba® once each day.
- If you want to change your usual diet, check with your doctor, pharmacist or nurse first as a
- change in diet may alter your need for insulin.
- Based on your blood sugar level your doctor may change your dose. Ask your healthcare provider what your insulin dose should be based on your blood sugar levels.
- When using other medicines, ask your doctor if your treatment needs to be adjusted.

For adults, inject Tresiba® subcutaneously once-daily at any time of day. For children with type 1 diabetes, inject Tresiba® subcutaneously at approximately the same time of the day.

Use in elderly patients (≥ 65 years old)
Tresiba® can be used in elderly patients. If you are elderly you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

If you have kidney or liver problems
If you have kidney or liver problems you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

Overdose:
If you use too much Tresiba® your blood sugar may get too low (hypoglycemia). See advice in section 'General effects from diabetes treatment/ Too low blood sugar (hypoglycemia)'.

If you think you, or a person you are caring for, have taken too much Tresiba®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss or are delayed in taking your dose of Tresiba®:
- Take your dose as soon as you remember and then continue with your regular dosing schedule.
- Make sure there are at least **8 hours** between your doses.

What are possible side effects from using Tresiba®?
These are not all the possible side effects you may have when taking Tresiba®. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people)
Too low blood sugar (hypoglycemia): If your blood sugar falls too low you may become unconscious. Very serious low blood sugar can cause brain damage and can cause death. If you have symptoms of low blood sugar, immediately take actions to increase your blood sugar. See advice in section 'General effects from diabetes treatment/Too low blood sugar (hypoglycemia)'.
Common (may affect up to 1 in 10 people)
Local reactions: Local reactions at the place you inject your insulin can occur. The reactions can include: pain, redness, hives, swelling, and itching. The reactions usually disappear after a few days. Talk to your doctor if the reactions do not disappear after a few weeks. Stop using

Tresiba® and immediately talk to your doctor if the reactions become serious. For more information, see 'Serious allergic reaction'.

Uncommon (may affect up to 1 in 100 people)
Skin changes where you inject your insulin injection (lipodystrophy): Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject your insulin each time may reduce the risk of developing these skin changes. If you keep injecting your insulin in the same place of your body, these reactions can become more severe and affect the amount of insulin your body gets from the pen. If you notice these skin changes, talk to your doctor.

Swelling around your joints: When you first start using your insulin, your body may keep more water than it should. This can cause temporary swelling around your ankles and other joints.

Rare (may affect up to 1 in 1,000 people)
Tresiba® can cause allergic reactions such as hives, swelling of the tongue and lips, diarrhea, nausea, tiredness and itching.

Not known
Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy, pitted or thickened area. Change the injection site with each injection to help prevent these skin changes.

Serious allergic reaction: If you have a serious allergic reaction to Tresiba®, immediately stop using Tresiba® and immediately get emergency medical treatment. You may be having a serious allergic reaction if:

- The local reactions spread to other parts of your body.
- You suddenly feel unwell with sweating.
- You start being sick (vomiting).
- You experience difficulty in breathing.
- You experience a fast heartbeat or feeling dizzy.

General effects from diabetes treatment
Too low blood sugar (hypoglycemia)
Too low blood sugar can happen if you drink alcohol, use too much insulin, exercise more than usual, eat too little or miss a meal.

Warning signs of low blood sugar include headache; slurred speech; fast heartbeat; cold sweat, cool pale skin; feeling sick; feeling very hungry; tremor or feeling nervous or worried; feeling unusually tired, weak and sleepy; feeling confused, difficulty in concentrating; temporary changes in how well you see.

What to do if you get too low blood sugar:

- Eat glucose tablets (sugar tablets) or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets (sugar tablets) or a high sugar snack in case you feel the signs of having too low blood sugar).

- Rest and measure your blood sugar if possible. You may need to measure your blood sugar more than once, as it may take some time before your blood sugar improves.
- Wait until the signs of too low blood sugar have stopped or your blood sugar level has gotten better before continuing with your insulin as usual.

What others need to do if you pass out:
Tell everyone you spend time with that you have diabetes. Tell them what could happen if your blood sugar gets too low, including the risk of you passing out. Let them know that if you pass out, they must:
- Turn you on your side.
- Immediately get medical help.
- **Not** give you any food or drink because you may choke.

You may recover more quickly from passing out with an injection of glucagon. This can only be given to you by someone who knows how to give it.
- If you are given glucagon you will need sugar or a sugary snack as soon as you are able.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If not treated, severe low blood sugar can cause brain damage and cause death.

Talk to your doctor if:
- Your blood sugar got so low that you passed out.
- You have used an injection of glucagon.
- You have had too low blood sugar a few times recently.

These may mean that the amount or timing of your insulin injections, foods eaten, or exercise effort may need to be changed.

Too high blood sugar (hyperglycemia)
Too high blood sugar may happen if you eat more or exercise less than usual, drink alcohol, get an infection or a fever, have not used enough insulin, keep using less insulin than you need, forget to use your insulin or stop using insulin without talking to your doctor.

Warning signs for too high blood sugar include flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more than usual, feeling thirsty; losing your appetite, feeling or being sick (nausea or vomiting).

These may be signs of a very serious condition called ketoacidosis. This is a build-up of acid in the blood because the body is breaking down fat instead of sugar for energy. If not treated, ketoacidosis could lead to diabetic coma and death.

What to do if you get too high blood sugar:
- Check your blood sugar.
- Check your urine for ketones.
- Immediately talk to a doctor.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Too low blood sugar (hypoglycemia)	√		√
COMMON Reaction at administration site		√	
UNCOMMON Skin changes where you inject your insulin injection (lipodystrophy)		√	
Swelling around your joints		√	
RARE Serious allergic reaction		√	√
UNKNOWN Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use Tresiba® after the expiration date stated on the label. The expiry date refers to the last day of that month.

Do not store Tresiba® with the needle attached. Always safely remove and throw away the needle after each injection. This may help prevent contamination, infection and leakage. It also helps to make sure that you get the correct dose of Tresiba®.

Keep Tresiba® pen needles and all medicines out of the sight and reach of children.
Before first use
FlexTouch®: Store in a refrigerator (2°C to 8°C). Keep away from the freezing element. Do not freeze. Keep the cap on the pen in order to protect from light.
Penfill®: Store in a refrigerator (2°C to 8°C). Keep away from the freezing element. Do not

freeze.

After first opening or if carried as a spare
FlexTouch®: You can carry your Tresiba® pre-filled pen (FlexTouch®) with you and keep it at room temperature (not above 30°C) or in a refrigerator (2°C to 8°C) for up to 8 weeks (56 days). Always keep the cap on the pen when you are not using it in order to protect from light.
Penfill®: Do not refrigerate. You can carry your Tresiba® cartridge (Penfill®) with you and keep it at room temperature (not above 30°C) for up to 8 weeks (56 days). Always keep Tresiba® Penfill® in the outer carton when you are not using it in order to protect from light.

Keep out of reach and sight of children.

If you want more information about Tresiba®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling Novo Nordisk Canada Inc., at: 1-800-465-4334.

Tresiba®, Penfill®, FlexTouch®, NovoFine® and NovoFine® Plus are registered trademarks of Novo Nordisk A/S and used by Novo Nordisk Canada Inc.

This leaflet was prepared by Novo Nordisk Canada Inc.
Last Revised: 2022

Instructions on How to Use TRESIBA® 100/200 units/mL Solution for Injection in Pre-filled Pen (FlexTouch®)

Please read these instructions carefully before using your FlexTouch® pre-filled pen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Do not use the pen without proper training from your doctor or nurse.

Start by checking your pen to **make sure that it contains TRESIBA® 100/200 units/mL,** then look at the illustrations below to get to know the different parts of your pen and needle.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the FlexTouch® pre-filled pen.

TRESIBA® 100 units/mL: Your pen is a pre-filled dial-a-dose insulin pen containing 300 units of insulin. You can select a **maximum of 80 units per dose, in steps of 1 unit.** Your pen is designed to be used with NovoFine® or NovoFine® Plus single-use disposable needles up to a length of 8 mm. Needles are not included in the pack.

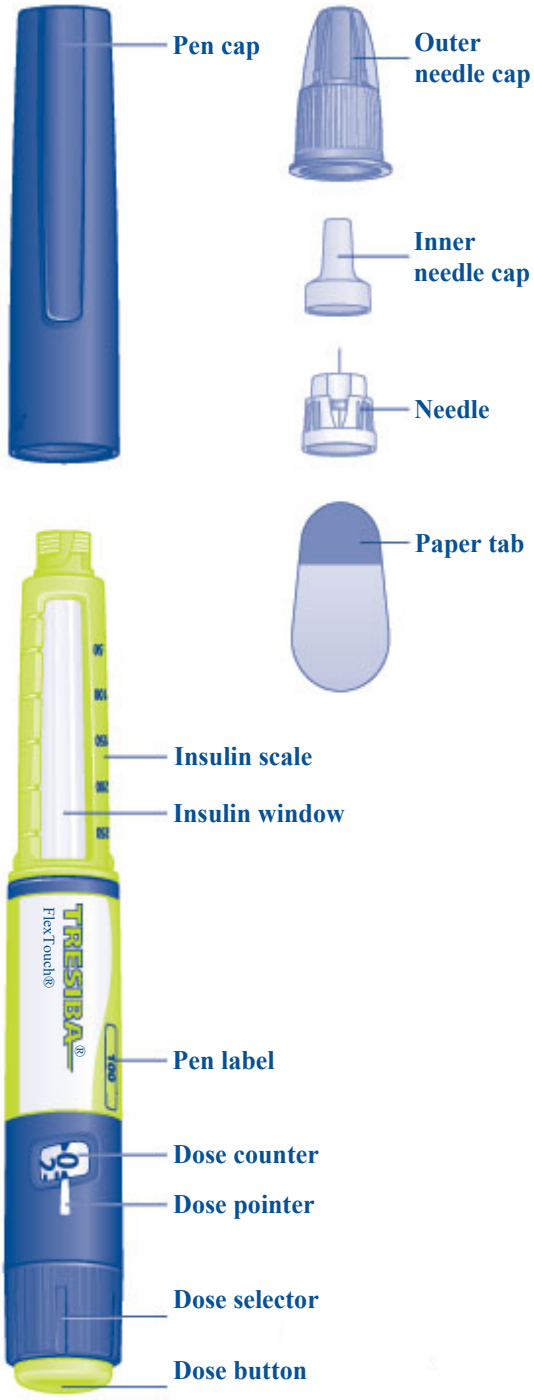
TRESIBA® 200 units/mL: Your pen is a pre-filled dial-a-dose insulin pen containing 600 units of insulin. You can select a **maximum of 160 units per dose, in steps of 2 units.** The dose counter of your pen shows the exact number of insulin units. **Do not make any dose re-calculation.** Your pen is designed to be used with NovoFine® or NovoFine® Plus single-use disposable needles up to a length of 8 mm. Needles are not included in the pack.

⚠ **Important information**

Pay special attention to these notes as they are important for correct use of the pen.

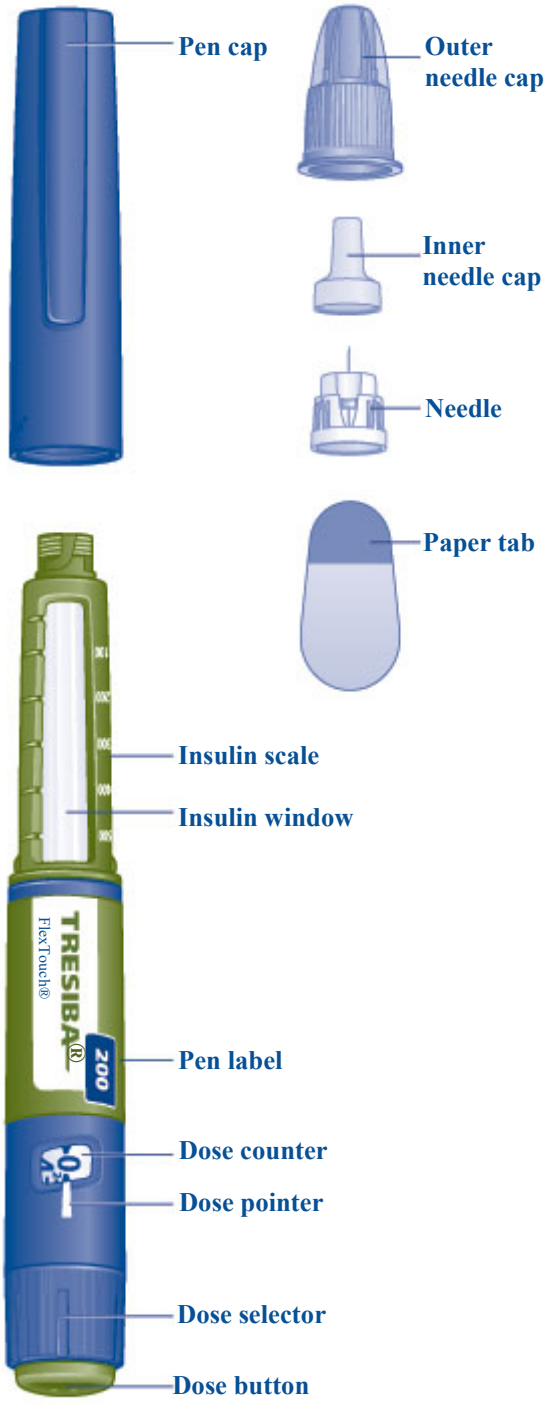
TRESIBA® FlexTouch® pen and needle (example)

(FlexTouch® 100 units/mL)



TRESIBA® FlexTouch® pen and needle (example)

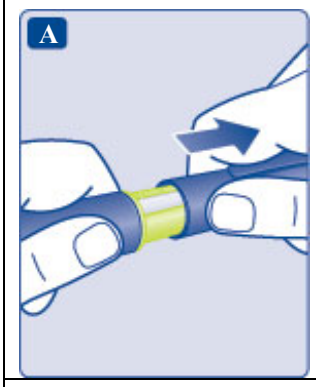
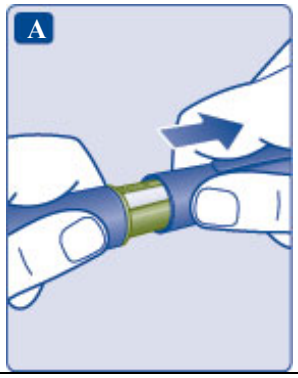
(FlexTouch® 200 units/mL)



1 Prepare Your Pen

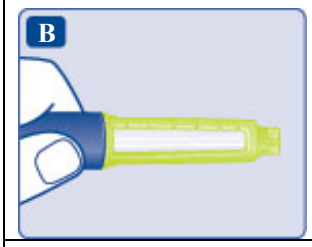
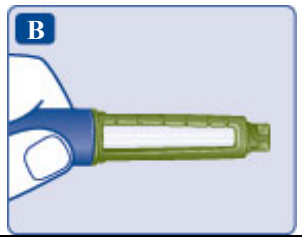
Check the name and strength on the label of your pen, to make sure that it contains TRESIBA® 100 or 200 units/mL. This is especially important if you take more than one type of insulin. If you take a wrong type of insulin, your blood sugar level may get too high or too low.

A) Pull off the pen cap.

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

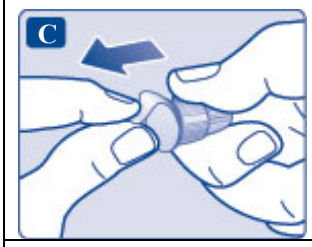
B) Check that the insulin in your pen is clear and colourless.

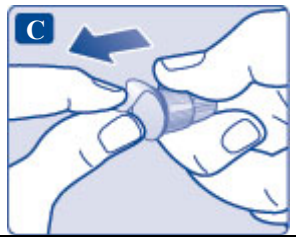
Look through the insulin window. If the insulin looks cloudy, do not use the pen.

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

C) Take a new needle and tear off the paper tab.

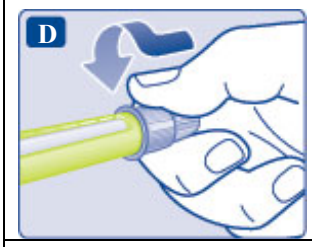
FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**



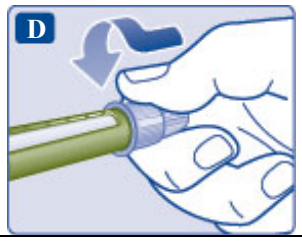


D) Push the needle straight onto the pen. Turn until it is on tight.

FlexTouch® 100 units/mL

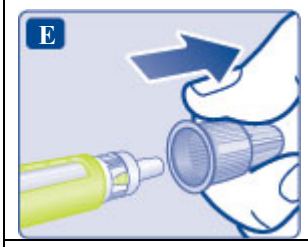


FlexTouch® 200 units/mL

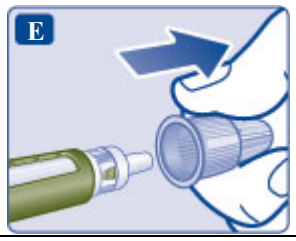


E) Pull off the outer needle cap and keep it for later. You will need it after the injection, to correctly remove the needle from the pen.

FlexTouch® 100 units/mL



FlexTouch® 200 units/mL

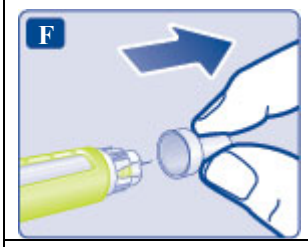


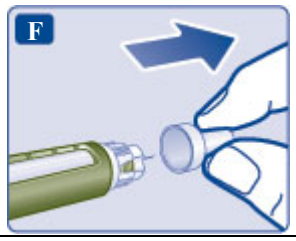
F) Pull off the inner needle cap and throw it away. If you try to put it back on, you may accidentally stick yourself with the needle.

A drop of insulin may appear at the needle tip. This is normal, but you must still check the insulin flow.

FlexTouch® 100 units/mL

FlexTouch® 200 units/mL





⚠ **Always use a new needle for each injection.**

This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

⚠ **Never use a bent or damaged needle.**

2 Check The Insulin Flow

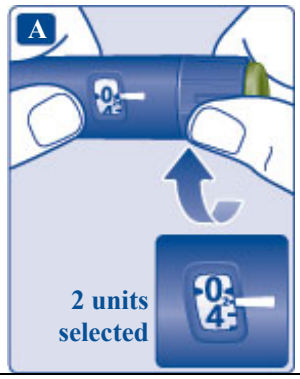
Always check the insulin flow before you start.

This helps you to ensure that you get your full insulin dose.

A) Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**

FlexTouch® 100 units/mL

FlexTouch® 200 units/mL

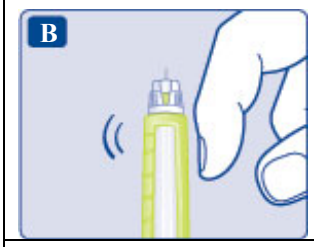


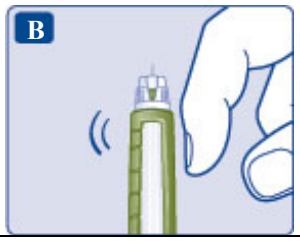
B) Hold the pen with the needle pointing up.

Tap the top of the pen gently a few times to let any air bubbles rise to the top.

FlexTouch® 100 units/mL

FlexTouch® 200 units/mL



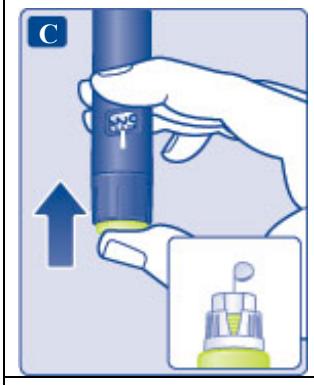


C) Press and hold in the dose button until the dose counter returns to 0.

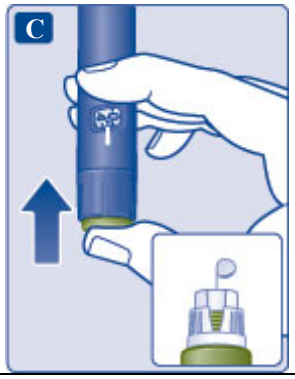
The 0 must line up with the dose pointer.

A drop of insulin should appear at the needle tip.

FlexTouch® 100 units/mL



FlexTouch® 200 units/mL



A small air bubble may remain at the needle tip, but it will not be injected.

If no drop appears, repeat steps 2**A** to 2**C** up to 6 times. If there is still no drop, change the needle and repeat steps 2**A** to 2**C** once more.

If a drop of insulin still does not appear, dispose of the pen and use a new one.

⚠ **Always make sure that a drop appears** at the needle tip before you inject. This makes sure that the insulin flows.
If no drop appears, you will **not** inject any insulin, even though the dose counter may move. This may indicate a blocked or damaged needle.

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

3 Select Your Dose

A) Make sure the dose counter shows 0 before you start.

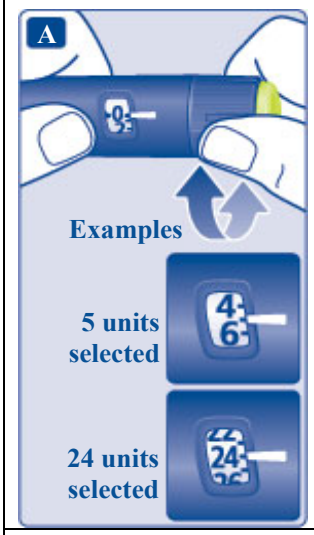
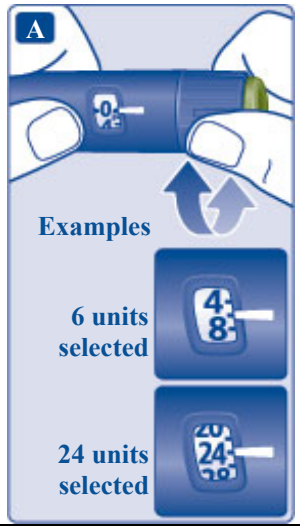
The 0 must line up with the dose pointer.

Turn the dose selector to select the dose you need, as directed by your doctor or nurse.

If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose.

For FlexTouch® 100 units/ mL, the pen can dial up to a maximum of 80 units.

For FlexTouch® 200 units/ mL, the pen can dial up to a maximum of 160 units. The dose counter shows the dose dialled in units. **Do not make any dose re-calculation.**

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

The dose selector changes the number of units. Only the dose counter and dose pointer will show how many units you select per dose.

For FlexTouch® 100 units/ mL, you can select up to 80 units per dose. When your pen contains less than 80 units, the dose counter stops at the number of units left.

For FlexTouch® 200 units/ mL, you can select up to 160 units per dose. When your pen contains less than 160 units, the dose counter stops at the number of units left.

The dose selector clicks differently when turned forwards, backwards or past the number of units left. Do not count the pen clicks.

⚠ **Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.**

Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low.

Do not use the insulin scale, it only shows approximately how much insulin is left in your

pen.

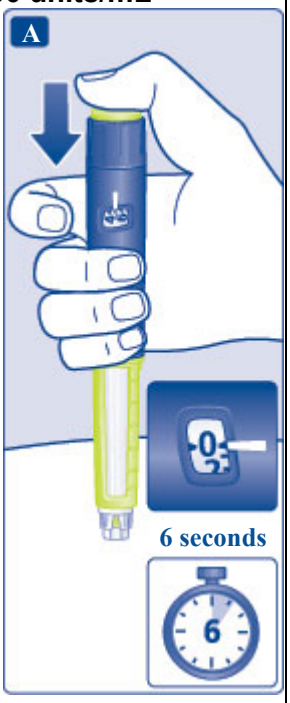
4 Inject Your Dose

A) Insert the needle into your skin as your doctor or nurse has shown you.

Make sure you can see the dose counter. Do not touch the dose counter with your fingers. This could interrupt the injection.

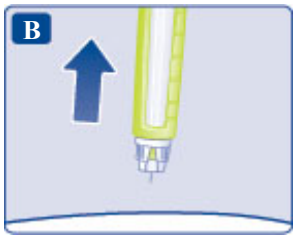
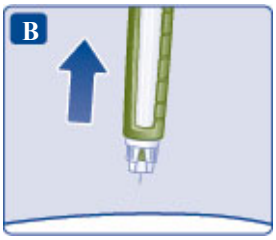
Press and hold down the dose button until the dose counter returns to 0. The 0 must line up with the dose pointer. You may then hear or feel a click.

Leave the needle under the skin for at least 6 seconds to make sure you get your full dose**.**

FlexTouch® 100 units/mL	FlexTouch® 200 units/mL
	

B) Pull the needle and pen straight up from your skin.

If blood appears at the injection site, press lightly with a cotton swab. Do not rub the area.

FlexTouch® 100 units/mL	FlexTouch® 200 units/mL
	

You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your dose.

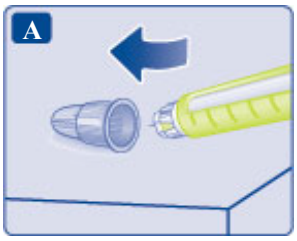
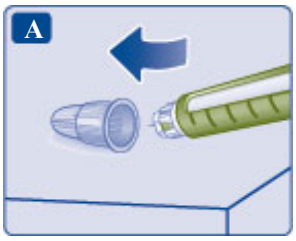
⚠ **Always watch the dose counter to know how many units you inject.**

The dose counter will show the exact number of units. Do not count the pen clicks.

Hold the dose button down until the dose counter returns to 0 after the injection. If the dose counter stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.

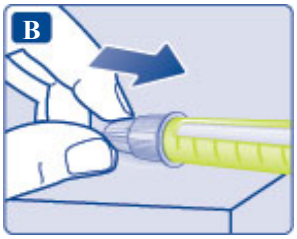
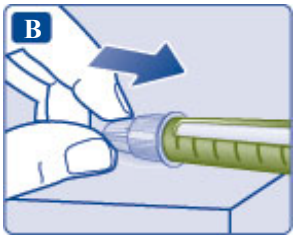
5 After Your Injection

A) Lead the needle tip into the outer needle cap on a flat surface without touching the needle or the outer cap.

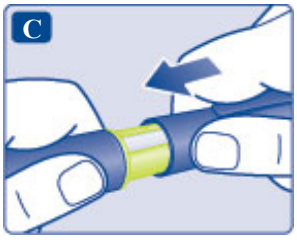
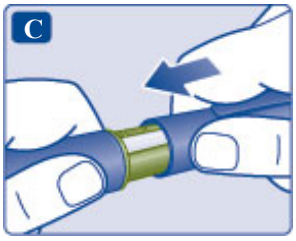
FlexTouch® 100 units/mL	FlexTouch® 200 units/mL
	

B) Once the needle is covered, **carefully push the outer needle cap completely on.**

Unscrew the needle and dispose of it carefully.

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

C) Put the pen cap on your pen after each use to protect the insulin from light.

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

Always dispose of the needle after each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. If the needle is blocked, you will **not** inject any insulin.

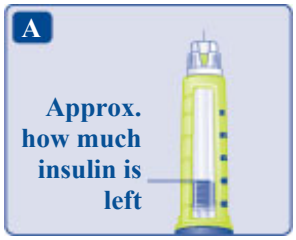
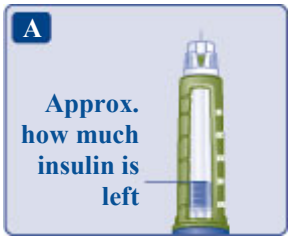
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

⚠ **Always remove the needle after each injection** and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

6 How Much Insulin Is Left?

A) The **insulin scale** shows you **approximately** how much insulin is left in your pen.

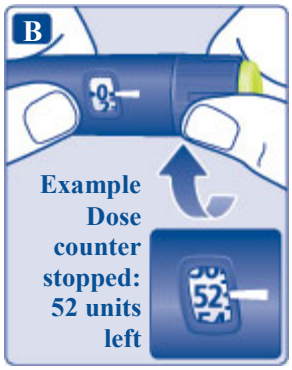
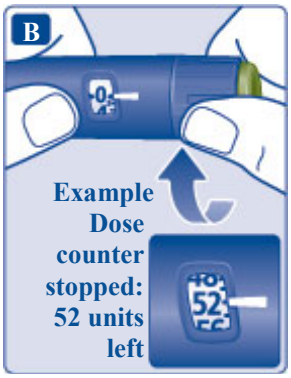
FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

B) To see precisely how much insulin is left, use the dose counter:

Turn the dose selector until the **dose counter stops.**

For FlexTouch® 100 units/ mL, if the pen shows 80, **at least 80** units are left in your pen. If it shows **less than 80**, the number shown is the number of units left in your pen.

For FlexTouch® 200 units/ mL, if the pen shows 160, **at least 160** units are left in your pen. If it shows **less than 160**, the number shown is the number of units left in your pen.

FlexTouch® 100 units/mL	**FlexTouch® 200 units/mL**
	

Turn the dose selector back until the dose counter shows 0.

If you need more insulin than the units left in your pen, you can split your dose between two pens.

⚠ **Be very careful to calculate correctly if splitting your dose.**

If in doubt, take the full dose with a new pen. If you split the dose wrong, you will inject too little or too much insulin, which can lead to too high or too low blood sugar level.

⚠ **Further important information**

Always keep your pen with you.

Always carry an extra pen and new needles with you, in case of loss or damage.

Always keep your pen and needles **out of sight and reach of others,** especially children

Never share your pen or your needles with other people. It might lead to cross-infection

Never share your pen with other people. Your medicine might be harmful to their health.

Caregivers must **be very careful when handling used needles** – to reduce the risk of needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

Do not leave the pen in a car or other place where it can get too hot or too cold.

Do not expose your pen to dust, dirt or liquid.

Do not wash, soak or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

Do not drop your pen or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the insulin flow before you inject.

Do not try to refill your pen. Once empty, it must be disposed of.

Do not try to repair your pen or pull it apart.