PROFESSIONAL INFORMATION FOR TRESIBA® 100 U/ML AND TRESIBA® 200 U/ML

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

Tresiba® 100 U/ml, solution for injection.

Tresiba® 200 U/ml, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tresiba® 100 U/ml

Contains insulin degludec * 100 U/ml

(equivalent to salt-free anhydrous insulin degludec 3,66 *mg)*

Excipients with known effect:

Preservatives

Phenol	0,150 *% m/v*
Metacresol	0,172 *% m/v*

Sugar free.

One pre-filled pen or Penfill® cartridge contains 3 *ml* equivalent to 300 *units* insulin degludec. The pre-filled pen can provide a maximum dose of 80 *units* in a single injection in dose increments of 1 *unit*.

Tresiba® 200 U/ml

Contains insulin degludec * 200 *U/ml*

(equivalent to salt-free anhydrous insulin degludec 7,32 *mg*)

Excipients with known effect:

Preservatives

Phenol 0,150 *% m/v*

Metacresol 0,172 *% m/v*

Sugar free.

One pre-filled pen contains 3 ml equivalent to 600 *units* insulin degludec.

The pre-filled pen can provide a maximum dose of 160 *units* in a single injection in dose increments of 2 *units*.

*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology. For the full list of excipients, see *section 6.1*.

3 PHARMACEUTICAL FORM

Solution for injection.

Tresiba® is a colourless solution free from turbidity and particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year, as basal add-on co-medication in patients who are inadequately controlled:

- In type 1 diabetes mellitus, Tresiba® should be used with short-acting soluble insulin at the meal times.
- In type 2 diabetes mellitus, Tresiba® should be used as an add-on to oral antidiabetic medicines with or without the use of short acting insulin at meal times.

4.2 Posology and method of administration

Posology

Tresiba® is a recombinant ultra-long-acting basal insulin for once-daily subcutaneous administration at any time of the day. Insulin degludec has a slow consistent rate of absorption which provides a flat and stable glucose-lowering-effect resulting in a low variability of the glucose-lowering-effect. When needed, the patient has the option of changing the once daily injection time from day-to-day.

Tresiba® is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.

In patients with type 2 diabetes mellitus, Tresiba® can be administered alone or in any combination with oral antidiabetic medicines, GLP-1 receptor agonists and bolus insulin. (See *section 3.1*).

In type 1 diabetes mellitus, Tresiba® must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.

An adjustment of insulin dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

The potency of Tresiba® is expressed in units (*U*). One unit (*U*) insulin degludec corresponds to one international unit (*IU*) of insulin human and to one unit of all other insulin analogues.

Initiation of Tresiba®

For patients with type 2 diabetes mellitus, the recommended daily starting dose of Tresiba® is 10 units, followed by individual dosage adjustments.

For patients with type 1 diabetes mellitus, Tresiba® is to be used once-daily with mealtime insulin and requires subsequent individual dosage adjustments.

Transfer from other insulin products

For patients with type 2 diabetes taking basal, basal-bolus, premix or self-mixed insulin therapy, changing the basal insulin to Tresiba® can be done unit-to-unit based on the previous basal insulin dose followed by individual dosage adjustments.

For most patients with type 1 diabetes, changing the basal insulin to Tresiba® can be done unit-to-unit based on the previous basal insulin dose with subsequent individual dosage adjustments. For patients with type 1 diabetes transferring from twice-daily basal insulin or having HbA_{1c} < 8,0 % at the time of transfer, the dose of Tresiba® needs to be determined on an individual basis. Dose reduction needs to be considered followed by individual dosage adjustment based on the glycaemic response.

Close glucose monitoring is recommended during the transfer and 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.

Flexibility in dosing time

Based on the needs of the patient, Tresiba® allows for flexibility in the timing of insulin administration. Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule. Ensure a minimum of 8 hours between injections.

Tresiba® 200 U/ml

Regardless of which degludec product is used, the needed dose is dialled in units. Tresiba® 200 U/ml prefilled pen provides the dose in half the volume of standard basal insulin products (100 units/ml) and can provide doses up to 160 units in a single injection.

Tresiba® should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use of Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus

In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral anti diabetic medicines, GLP-1 receptor agonists and bolus insulin.

When adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

When adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20 % to minimise the risk of hypoglycaemia.

Subsequently, dosage should be adjusted.

Elderly

Tresiba® can be used in elderly patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis. (See *section 5.2*)

Renal and hepatic impaired patients

Tresiba® can be used in renal and hepatic impaired patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis. (See *section 5.2*)

Paediatric population

Tresiba® can be used in adolescents and children from the age of 1 year. When changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia (see *section 4.4*).

Method of administration

Tresiba® is for subcutaneous administration only.

Tresiba® must not be administered intravenously as it may result in severe hypoglycaemia.

Tresiba® must not be administered intramuscularly as it may change the absorption.

Tresiba® is not to be used in insulin infusion pumps.

Tresiba® is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see *sections 4.4 and 4.8*).

Tresiba® must not be used if the solution does not appear clear and colourless.

Tresiba® which has been frozen must not be used and should be discarded.

The injection needles are to be discarded after each injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *section 6.1.*

4.4 Special warnings and precautions for use

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see *sections 4.5, 4.8 and 4.9*).

Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Patients whose blood-glucose control is improved (e.g., by intensified insulin therapy) may experience a decreased sensitivity to usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms of hypoglycaemia may disappear in patients with long-standing diabetes.

Concomitant illness, especially infections and conditions with fever, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.
The prolonged effect of Tresiba® may delay recovery from hypoglycaemia.

In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.

Hyperglycaemia

Tresiba® should not be used to treat severe hyperglycaemia

Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.

Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes mellitus, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Transfer from other insulin medicinal products

Transferring a patient to another type, brand or manufacturer of insulin must be done under medical supervision and may result in the need for a change in dosage.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. 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.

Immune system disorder

With Tresiba® allergic reactions may occur. Immediate-type allergic reaction to either insulin itself or the excipients may potentially be life threatening. With Tresiba® hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported with rare frequency.

Injection site reaction

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with Tresiba®.

Combination of thiazolidinediones (TZDs) and Tresiba®

Cases of congestive heart failure have been reported when thiazolidinediones (also known as glitazones) were used in combination with insulin, especially in patients with risk factors for development of congestive heart failure. This should be kept in mind if treatment with the combination of thiazolidinediones and Tresiba® is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema. Thiazolidinediones must be discontinued if any signs of deterioration in cardiac function occur.

Insulin initiation and glucose control intensification

Intensification or rapid improvement in glucose control has been associated with transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycaemic control decreases the risk of diabetic retinopathy and neuropathy.

Eye disorder

Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Avoidance of medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba® as well as other insulin products. Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

To avoid dosing errors and potential overdose, patients and healthcare professionals should never use a syringe to draw the medicinal product from the cartridge in the pre-filled pen.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet *(see section 6.6).*

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Paediatric population

Tresiba® has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties. Safety and efficacy have been demonstrated in a long term trial in children aged 1 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population.

Other special populations

Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in the elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

Combination with thiazolidinediones (TZDs): Please refer to *section 4.4* for the possibility of the development of congestive heart failure.

The following substances may reduce the insulin requirement:

Oral antidiabetic medicinal products, Glucagon-like peptide-1 (GLP-1) receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.

The following substances may increase the insulin requirement:

Oral contraceptive, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormones and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin

4.6 Fertility, pregnancy and lactation

Pregnancy

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 meal time insulin (EXPECT).

Tresiba® was non-inferior to insulin detemir as measured by HbA_{1c} at last planned HbA_{1c} visit prior to delivery after GW 16. Moreover, no difference between treatment groups was observed for glycaemic control (change in HbA_{1c}, FPG and PPG) during pregnancy (Table 1).

No clinically relevant differences were observed between Tresiba® and insulin detemir for the maternal safety endpoints (hypoglycaemia, pre-term delivery, pre-eclampsia, non-planned

caesarean section and adverse events during the pregnancy). The majority of the adverse events reported in both the groups were non-serious, mild in severity, unlikely related to the trial product and had the outcome “recovered/resolved”. No deaths were reported in the subjects who were randomised in the trial.

No perinatal or neonatal death was reported. No clinically relevant differences were observed between Tresiba® and insulin detemir for the pregnancy endpoints (early foetal death, presence of major abnormalities, neonatal hypoglycaemia, perinatal mortality, neonatal mortality, foetal macrosomia, large for gestational age, and adverse events in the infant during the 30 days after birth).

Table 1 Results from the open-label, randomised active controlled clinical trial in pregnant women with type 1 diabetes mellitus

	Tresiba®	**Insulin detemir**
Full Analysis Set for pregnant women (N)	92	96
HbA_{1c} (%) at treatment baseline		
N	87	90
Mean (SD)	6.73 (0.65)	6.56 (0.77)
HbA_{1c} (%) at last planned visit prior to delivery		
N	84	84
Mean (SD)	6.30 (0.70)	6.26 (0.73)
Estimated treatment difference	*-0.11%-points [-0.31; 0.08]$_{95\%CI}$; p<0.0001*	
HbA_{1c} ⩽ 6.0% - in-trial pregnancy period – treatment baseline		
N	87	90
Percentage of subjects	12.6	28.9
HbA_{1c} ⩽ 6.0% - in-trial pregnancy period- at last planned visit prior to delivery		
N	84	84
Percentage of subjects	42.9	36.9
Estimated odds ratio	*1.95 [0.92; 4.17]$_{95\%CI}$, p = 0.0832*	
HbA_{1c} ⩽ 6.5% - in-trial pregnancy period – treatment baseline		

N	87	90
Percentage of subjects	39.1	45.6
HbA_{1c} ⩽ 6.5% - in-trial pregnancy period- at last planned visit prior to delivery		
N	84	84
Percentage of subjects	69.0	63.1
Estimated odds ratio	*2.05 [0.97; 4.33]$_{95\%CI}$, p = 0.0617*	
FPG (mmol/L) at treatment baseline		
N	87	90
Mean (SD)	8.15 (3.68)	7.64 (3.03)
FPG (mmol/L) at last planned visit prior to delivery		
N	82	83
Mean (SD)	6.17 (2.05)	6.79 (2.47)
Estimated treatment difference	*-0.69 mmol/L [-1.42; 0.04]$_{95\%CI}$, p = 0.0652*	
Average PPG (mmol/L) at treatment baseline		
N	85	88
Mean (SD)	7.45 (2.02)	7.58 (2.23)
Average PPG (mmol/L) at last planned visit prior to delivery		
N	74	70
Mean (SD)	7.37 (1.35)	6.96 (1.63)
Estimated treatment difference	*0.44 mmol/L [-0.13; 1.00]$_{95\%CI}$, p = 0.1277*	
Safety analysis set pregnant women – pregnancy period		
Number of subjects with at least one hypoglycaemic episode	89 (97.8%)	91 (96.8%)
Number of events	5431	5982
Rate per 100 years of exposure	11,844.9	13,401.2

The results from the EXPECT trial indicate that Tresiba® is not associated with an excess risk of adverse pregnancy outcomes, when compared to insulin detemir, in women with pre-existing diabetes.

In a prospective non-interventional post-authorisation safety study (EVOLVE), pregnant women with type 1 or type 2 diabetes exposed to insulin detemir (n=727) or other basal insulins (n=730)

were monitored for adverse pregnancy outcomes. A subset of patients in this study were exposed to Tresiba® (n=41). No safety concerns were observed for the subgroup treated with Tresiba®.

The use of Tresiba® in pregnant women with diabetes has been investigated

in an interventional trial and as part of a prospective non-interventional study (see *section 4.6*). The use of Tresiba® during pregnancy has not shown any foetal malformation or foeto/neonatal toxicity. The treatment with Tresiba® may be considered during pregnancy, if clinically needed.

Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.

In general, intensified blood glucose control and 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 trimesters. After delivery, insulin requirements usually return rapidly to pre-pregnancy values.

Breast-feeding

There is no clinical experience with Tresiba® during breast-feeding. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma.

It is unknown whether insulin degludec is excreted in human milk. No metabolic effects are anticipated in the breast-fed newborn/infant.

Fertility

Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery).

Patients need to be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia.

4.8 Undesirable effects

a. Summary of the safety profile

More than 5600 patients have been exposed to Tresiba® in the clinical development program. The most frequently reported adverse reaction during treatment is hypoglycaemia.

b. Tabulated list of adverse reactions (Table 2)

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

System organ class	Preferred term	Frequency
General disorders and administration site conditions	*Common:* Injection site reactions	2,4 %
	Uncommon: Peripheral oedema	0,4 %
Immune system disorders	*Rare:* Hypersensitivity	0,05 %
	Rare: Urticaria	0,05 %
Metabolism and nutrition disorders	*Very common:* Hypoglycaemia	93,0 % - 99,4 % in subjects with type 1 diabetes, 17,3 % to 81,9 % in subjects with type 2 diabetes
Skin and subcutaneous tissue disorders	*Uncommon:* Lipodystrophy	0,2 %

ADRs from postmarketing sources

Adverse reactions listed below are based on postmarketing source data and classified according to MedDRA System Organ Class. (*Table 3*)

System organ class	Preferred term	Frequency
Skin and subcutaneous tissue disorders	Cutaneous amyloidosis †	Not known

† ADR from postmarketing sources.

c. Description of selected adverse reactions

Immune system disorders

With insulin preparations, allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.

With Tresiba®, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see *section 4.4*).

Injection site reactions

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with Tresiba®. These reactions are usually mild and transitory and they normally disappear during continued treatment.

d. Paediatric population

Tresiba® has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see *section 5.2*). Safety and efficacy have been demonstrated in a long term trial in children aged 1 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population (see s*ection 5.1*).

e. Other special populations

Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in elderly and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

A specific overdose cannot be defined. However, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required. (See *section 4.4*).

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

glucose-containing products.

- Severe hypoglycaemic episodes, where the patient is not able to treat himself, 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 health care 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting. ATC code: A10AE06. (A 21.1 Insulin Preparations)

Mechanism of action

Insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

The blood glucose-lowering effect of insulin is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Pharmacodynamic effects

Insulin degludec is an ultra-long-acting basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering effect of Tresiba® (see

figure 1). During a period of 24 hours with once-daily treatment, the glucose-lowering effect of Tresiba®, in contrast to insulin glargine, was evenly distributed between the first and second 12 hours ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,total,SS} = 0,5$).

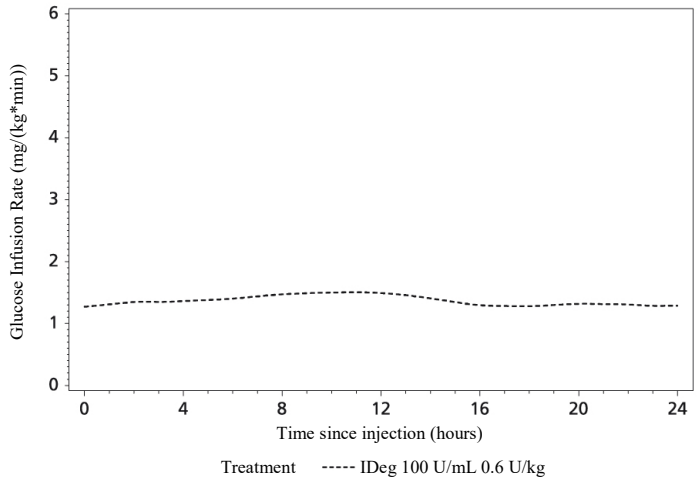


Figure 1 Mean Glucose Infusion (GIR) profile – insulin degludec at steady- state in type 2 diabetes mellitus.

The duration of action of insulin degludec is beyond 42 hours within the therapeutic dose range. Steady state will occur after 2 – 3 days of dose administration.

The insulin degludec glucose-lowering action at steady state shows a low day-to-day variability in terms of Co-efficients of Variation (CV) for the glucose-lowering effect during 0 - 24 *hours* ($AUC_{GIR,\tau,SS}$) and 2 - 24 hours ($AUC_{GIR2\text{-}24h,SS}$).

The total glucose-lowering-effect of insulin degludec increases linearly with increasing doses. The total glucose-lowering-effect is comparable for insulin degludec 100 *U/ml* and 200 *U/ml* when each is administered at the same doses of the two products.

Clinical efficacy and safety

There is no clinically relevant difference in the pharmacodynamics of insulin degludec between elderly and younger adult subjects.

There is no clinically relevant development of insulin antibodies after long-term treatment with insulin degludec.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation.

Steady-state serum concentration is reached after 2–3 days of daily Tresiba® administration.

During a period of 24 hours with once-daily treatment, the exposure of insulin degludec was evenly distributed between the first and second 12 hours. The ratio between $AUC_{IDeg,0\text{-}12h,SS}$ and $AUC_{IDeg,T,SS}$ was 0.5.

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma.

Biotransformation

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

Elimination

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

Linearity

Dose proportionality in total exposure is observed after subcutaneous administration within the therapeutic dose range. In direct comparison, requirements for bioequivalence are met for Tresiba® 100 units/mL and Tresiba® 200 units/mL (based on $AUC_{IDeg,\tau,SS}$ and $C_{max,IDeg,SS}$).

Elderly, renal and hepatic impairment

There is no difference in the pharmacokinetics of insulin degludec between elderly and younger adult patients, between races or between healthy subjects and patients with renal or hepatic impairment.

Paediatric population

Pharmacokinetic properties of insulin degludec in children (1-11 years) and adolescents (12-18 years) were at steady state comparable to those observed in adults with type 1 diabetes mellitus. Total exposure after a single dose was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.

5.3 Preclinical safety data

Non-clinical data reveal no safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction.

The ratio of mitogenic relative to metabolic potency for insulin degludec is comparable to that of human insulin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Metacresol

Phenol

Zinc acetate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with any other medicinal products. Substances added to Tresiba® may cause degradation of insulin degludec.

Tresiba® must not be added to infusion fluids.

6.3 Shelf life

30 months.

Tresiba® 100 U/ml FlexTouch®

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 8 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C). Keep the cap on the pen in order to protect from light.

Tresiba® 200 U/ml FlexTouch®

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 8 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C). Keep the cap on the pen in order to protect from light.

Tresiba® 100 U/ml Penfill®

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 8 weeks. Do not store above 30°C. Do not refrigerate. Keep cartridges in the outer carton in order to protect from light.

6.4 Special precautions for storage

Before use:

Store in a refrigerator (2 ℃ – 8 ℃) but away from the freezing element.

Do not freeze.

In-use or carried as a spare:

Store at or below 30 ℃.

Tresiba® 100 *U/ml* FlexTouch® and Tresiba® 200 *U/ml* FlexTouch®:

Keep the pen cap on when Tresiba® is not in use in order to protect from light.

Can be stored in a refrigerator.

For storage conditions after first opening of the medicinal product, see *section 6.3.*

Tresiba® 100 *U/ml* Penfill®:

Keep cartridges in the outer carton in order to protect from light.

Do not refrigerate.

Tresiba® FlexTouch® and Tresiba® Penfill® can be used for up to 8 weeks.

Discard any unused portion after 8 weeks of use.

6.5 Nature and contents of container

Tresiba® 100 U/ml

Penfill®: 3 *ml* solution in a cartridge made of clear, colourless type 1 glass with a red plunger (halobutyl) and a cream stopper (halobutyl/polyisoprene). The cartridge is packaged in press through blister pack made of aluminium foil and polyethylene terephthalate (PET). The blister is packed in a carton box.

Pack size: 1, 5 and 10 x 3 *ml*

FlexTouch®: 3 *ml* solution in a cartridge made of clear, colourless type 1 glass with a red plunger (halobutyl) and a cream stopper (halobutyl/polyisoprene) contained in a

prefilled multidose disposable pen made of polypropylene. The pen(s) is/are packed in a carton box.

Pack sizes (100 *units/ml*): 1 x 3 *ml*, 1 x 3 *ml* (including needle pack), 5 x 3 *ml*, multipack: 2 x (5 x 3 *ml*).

Tresiba® 200 U/ml

FlexTouch®: 3 *ml* solution in a cartridge made of clear, colourless type 1 glass with a red plunger (halobutyl) and a cream stopper (halobutyl/polyisoprene) contained in a prefilled multi-dose disposable pen made of polypropylene.
The pen(s) is/are packed in a carton box.

Pack sizes: 1 x 3 *ml*, 1 x 3 *ml* (including needle pack), 2 x 3 *ml*, 3 x 3 *ml*, 5 x 3 *ml*, multipack: 2 x (5 x 3 *ml*).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for use by one person only. It must not be refilled.

Tresiba® must not be used if the solution does not appear clear and colourless.

Tresiba® which has been frozen must not be used.

A new needle must always be attached before each use. Needles must not be re-used. The patient should discard the needle after each injection.

In the event of blocked needles, patients must follow the instructions described in the instructions for use.

Any waste material should be disposed of in accordance with local requirements.

For detailed instructions for use, see the instructions for use.

Tresiba® FlexTouch® is available in two strengths. “Tresiba® 100 U/ml” or “Tresiba® 200 U/ml” is clearly marked on the pen label and packaging.

Tresiba® 100 U/ml FlexTouch®

The packaging and label are light green.

The product is designed to be used with NovoFine®/NovoTwist® injection needles up to a length of 8 mm. It delivers 1 – 80 units in steps of 1 unit. Detailed instructions accompanying the pre-filled pen must be followed.

Tresiba® 200 U/ml FlexTouch®

The packaging and label are dark green with striping with a red box highlighting the formulation strength.

The product is designed to be used with NovoFine®/NovoTwist® injection needles up to a length of 8 mm. It delivers 2 – 160 units in steps of 2 units. Detailed instructions accompanying the pre-filled pen must be followed.

Tresiba® 100 U/ml Penfill®

The product is designed to be used with Novo Nordisk delivery systems (durable devices for repeated use not included in the pack) and NovoFine®/NovoTwist® injection needles up to a length of 8 mm. Detailed instructions accompanying the delivery system must be followed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2196

8 REGISTRATION NUMBER (S)

Tresiba® 100 U/ml: 47/21.1/0108

Tresiba® 200 U/ml: 47/21.1/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 26 November 2015

10 DATE OF REVISION OF THE TEXT

Date of revision: 23 August 2022