Tresiba®

FlexTouch®

100 units/ml
Solution for injection in pre-filled pen.

Qualitative and quantitative composition

1 ml solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).
One pre-filled pen contains 300 units of insulin degludec in 3 ml solution.
*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.
For the full list of excipients see *List of excipients*.

Pharmaceutical form

Solution for injection (FlexTouch®).
Clear, colourless, neutral solution.

Therapeutic indications

Treatment of diabetes mellitus in adults.

Posology and method of administration

Posology

Tresiba® is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day.
The potency of insulin analogues, including insulin degludec, is expressed in units (U). One (1) unit (U) of insulin degludec corresponds to 1 international unit (IU) of human insulin, 1 unit of insulin glargine or 1 unit of insulin detemir.
In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, in combination with oral anti-diabetic medicinal products as well as in combination with bolus insulin (see *Pharmacodynamic properties*).
In type 1 diabetes mellitus, Tresiba® must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.
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.
As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Tresiba® 100 units/ml and Tresiba® 200 units/ml
Tresiba® is available in two strengths. For both, the needed dose is dialled in units. The dose steps, however, differ between the two strengths of Tresiba®.
With Tresiba® 100 units/ml a dose of 1–80 units per injection, in steps of 1 unit, can be administered.
With Tresiba® 200 units/ml a dose of 2–160 units per injection, in steps of 2 units, can be administered. The dose is provided in half the volume of 100 units/ml basal insulin products.
The dose counter shows the number of units regardless of strength and **no** dose conversion should be done when transferring a patient to a new strength.

Flexibility in dosing time
On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration (see *Pharmacodynamic properties*). A minimum of 8 hours between injections should always be ensured.
Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule.

Initiation

Patients with type 2 diabetes mellitus
The recommended daily starting dose is 10 units followed by individual dosage adjustments.

Patients with type 1 diabetes mellitus
Tresiba® is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments.

Transfer from other insulin medicinal products

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 anti-diabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus
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.

Patients with type 1 diabetes mellitus
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.

Special populations

Elderly (≥ 65 years old): Tresiba® can be used in elderly patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see *Pharmacokinetic properties*).

Renal and hepatic impairment: 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 *Pharmacokinetic properties*).

Paediatric population: The safety and efficacy of Tresiba® in children and adolescents below 18 years of age have not been established. Currently available data are described in *Pharmacokinetic properties,* but no recommendation on a posology can be made.

Method of administration

Tresiba® is for subcutaneous use 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® must not be used in insulin infusion pumps.
Tresiba® is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites are always to be rotated within the same region in order to reduce the risk of lipodystrophy.
Tresiba® comes in a pre-filled pen (FlexTouch®) designed to be used with NovoFine® or NovoTwist® injection needles.
The 100 units/ml pre-filled pen delivers 1–80 units in steps of 1 unit.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.
Patients whose blood-glucose control is greatly improved (e.g. by intensified insulin therapy) may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes.
Concomitant illness, especially infections and 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.
As with other basal insulin products, the prolonged effect of Tresiba® may delay recovery from hypoglycaemia.

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.

Combination of thiazolidinediones and insulin medicinal products

Cases of cardiac failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of cardiac 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 heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac symptoms occurs.

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.

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.

Interaction with other medicinal products and other forms of interaction

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

The following substances may reduce the insulin requirement
Oral anti-diabetic medicinal products, 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 contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the insulin requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with use of Tresiba® in pregnant women.
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.

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 using machines).
Patients must 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. The advisability of driving should be considered in these circumstances.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see *Description of selected adverse reactions* below).

Tabulated list of adverse reactions

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	*Frequency*
Immune system disorders	*Rare* - Hypersensitivity
	Rare - Urticaria
Metabolism and nutrition disorders	*Very common* - Hypoglycaemia
Skin and subcutaneous tissue disorders	*Uncommon* - Lipodystrophy
General disorders and administration site conditions	*Common* - Injection site reactions
	Uncommon - Peripheral oedema

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.

Lipodystrophy
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

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.

Paediatric population
Tresiba® has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see *Pharmacokinetic properties*). Safety and efficacy have not been investigated in children and adolescents.

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

Overdose

A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required.

- 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 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned.

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
Tresiba® is a 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).

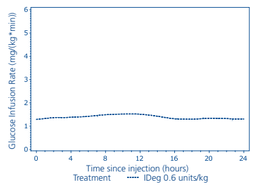


Figure 1 Glucose infusion rate profile, smoothed, steady state – Mean profile 0-24 hours – IDeg 100 units/ml 0.6 units/kg - Trial 1987

The duration of action of Tresiba® 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 four times lower day-to-day variability in terms of Coefficients of Variation (CV) for the glucose-lowering effect during 0-24 hours ($AUC_{GIR,T,SS}$) and 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$) as compared to insulin glargine, see Table 1.

Table 1 Day-to-day variability within-subjects in glucose-lowering effect of Tresiba® and insulin glargine at steady-state in subjects with type 1 diabetes mellitus.

	Insulin degludec (N26) (CV %)	Insulin glargine (N27) (CV %)
Day-to-day variability in glucose-lowering effect during one dosing interval ($AUC_{GIR,T,SS}$)	20	82
Day-to-day variability in glucose-lowering effect from 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$)	22	92

CV: within-subject coefficient of variation in %
SS: Steady State
$AUC_{GIR,2\text{-}24h}$: metabolic effect in last 22 hours of dosing interval (i.e., not influenced by i.v. insulin during the clamp run-in period)

Total glucose-lowering effect of Tresiba® increases linearly with increasing doses.
Total glucose-lowering effect is comparable for Tresiba® 100 units/ml and 200 units/ml after administration of same doses of the two products.
There is no clinically relevant difference in the pharmacodynamics of Tresiba® between elderly and younger adult subjects.

Clinical efficacy and safety

11 multi-national clinical trials of 26 or 52 weeks' duration were conducted as controlled, open label, randomised, parallel, treat-to-target trials exposing 4,275 patients to Tresiba® (1,102 in type 1 diabetes mellitus and 3,173 in type 2 diabetes mellitus).
The effect of Tresiba® was tested in patients with type 1 diabetes mellitus (Table 3), in insulin naïve patients (insulin initiation in type 2 diabetes mellitus, Table 4) and in previous insulin users (insulin intensification in type 2 diabetes mellitus, Table 5) with fixed as well as flexible dosing time (Table 6), and the reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior in all trials against all comparators (insulin detemir and insulin glargine). While improvements in HbA_{1c} were non-inferior compared to other insulin products, against sitagliptin Tresiba® was statistically significantly superior in reducing HbA_{1c} (Table 5). In a prospectively planned meta-analysis across seven treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, Tresiba® was superior in terms of a lower number of treatment emergent confirmed hypoglycaemic episodes (driven by a benefit in type 2 diabetes mellitus, see table 2) and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine (administered according to label). The reduction in hypoglycaemia was achieved at a lower average FPG level with Tresiba® than with insulin glargine.

Table 2 Hypoglycaemia meta-analysis outcomes

	Confirmed hypoglycaemia[a]	
Estimated risk ratio (Insulin degludec/Insulin glargine)	Total	Nocturnal
Type 1 + Type 2 diabetes mellitus (pooled)	0.91*	0.74*
Maintenance period [b]	0.84*	0.68*
Geriatric subjects ≥ 65 years	0.82	0.65*
Type 1 diabetes mellitus	1.10	0.83
Maintenance period [b]	1.02	0.75*
Type 2 diabetes mellitus	0.83*	0.68*
Maintenance period [b]	0.75*	0.62*
Basal only therapy in previously insulin-naïve	0.83*	0.64*

*Statistically significant [a] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/l or by the patient needing third party assistance. Confirmed nocturnal hypoglycaemia was defined as episodes between midnight and 6 a.m. [b] Episodes from week 16.

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

Table 3 Results from clinical trials in type 1 diabetes mellitus.

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	**Insulin glargine[1]**	**Tresiba®[1]**	**Insulin detemir[1]**
N	**472**	**157**	**302**	**153**
HbA_{1c} (%)				
End of trial	7.3	7.3	7.3	7.3
Mean change	-0.40	-0.39	-0.73	-0.65
	Difference: -0.01 [-0.14; 0.11]		*Difference: -0.09 [-0.23; 0.05]*	
FPG (mmol/l)				
End of trial	7.8	8.3	7.3	8.9
Mean change	-1.27	-1.39	-2.60	-0.62
	Difference: -0.33 [-1.03; 0.36]		*Difference: -1.66 [-2.37; -0.95]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe	0.21	0.16	0.31	0.39
Confirmed[2]	42.54	40.18	45.83	45.69
	Ratio: 1.07 [0.89; 1.28]		*Ratio: 0.98 [0.80; 1.20]*	
Confirmed nocturnal[2]	4.41	5.86	4.14	5.93
	Ratio: 0.75 [0.59; 0.96]		*Ratio: 0.66 [0.49; 0.88]*	

[1] In a once daily regimen + insulin aspart to cover mealtime insulin requirements.
[2] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/l or by the patient needing third party assistance. Confirmed nocturnal hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 4 Results from clinical trials in insulin naïve type 2 diabetes mellitus (insulin initiation).

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	**Insulin glargine[1]**	**Tresiba®[1]**	**Insulin glargine[1]**
N	**773**	**257**	**228**	**229**
HbA_{1c} (%)				
End of trial	7.1	7.0	7.0	6.9
Mean change	-1.06	-1.19	-1.30	-1.32
	Difference: 0.09 [-0.04; 0.22]		*Difference: 0.04 [-0.11; 0.19]*	
FPG (mmol/l)				
End of trial	5.9	6.4	5.9	6.3
Mean change	-3.76	-3.30	-3.70	-3.38
	Difference: -0.43 [-0.74; -0.13]		*Difference: -0.42 [-0.78; -0.06]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe	0	0.02	0	0
Confirmed[2]	1.52	1.85	1.22	1.42
	Ratio: 0.82 [0.64; 1.04]		*Ratio: 0.86 [0.58; 1.28]*	
Confirmed nocturnal[2]	0.25	0.39	0.18	0.28
	Ratio: 0.64 [0.42; 0.98]		*Ratio: 0.64 [0.30; 1.37]*	

[1] Once-daily regimen + metformin ± DPP-IV inhibitor.
[2] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/l or by the patient needing third party assistance. Confirmed nocturnal hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 5 Results from clinical trials in type 2 diabetes mellitus: left – prior basal insulin users, right – insulin naïve.

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	**Insulin glargine[1]**	**Tresiba®[2]**	**Sitagliptin[2]**
N	**744**	**248**	**225**	**222**
HbA_{1c} (%)				
End of trial	7.1	7.1	7.2	7.7
Mean change	-1.17	-1.29	-1.56	-1.22
	Difference: 0.08 [-0.05; 0.21]		*Difference: -0.43 [-0.61; -0.24]*	
FPG (mmol/l)				
End of trial	6.8	7.1	6.2	8.5
Mean change	-2.44	-2.14	-3.22	-1.39
	Difference: -0.29 [-0.65; 0.06]		*Difference: -2.17 [-2.59; -1.74]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe hypoglycaemia	0.06	0.05	0.01	0
Confirmed[3]	11.09	13.63	3.07	1.26
	Ratio: 0.82 [0.69; 0.99]		*Ratio: 3.81 [2.40; 6.05]*	
Confirmed nocturnal[3]	1.39	1.84	0.52	0.30
	Ratio: 0.75 [0.58; 0.99]		*Ratio: 1.93 [0.90; 4.10]*	

[1] Once-daily regimen + insulin aspart to cover mealtime insulin requirements ± metformin ± pioglitazone.
[2] Once-daily regimen ± metformin SU/glinide ± pioglitazone.
[3] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/l or by the patient needing third party assistance. Confirmed nocturnal hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 6 Results from a clinical trial with flexible dosing of Tresiba® in type 2 diabetes mellitus.

	26 weeks of treatment		
	Tresiba®[1]	**Tresiba® Flex[2]**	**Insulin glargine[3]**
N	**228**	**229**	**230**
HbA_{1c} (%)			
End of trial	7.3	7.2	7.1
Mean change	-1.07	-1.28	-1.26
	Difference: -0.13 [-0.29; 0.03][5]		*Difference: 0.04 [-0.12; 0.20]*
FPG (mmol/l)			
End of trial	5.8	5.8	6.2
Mean change from baseline	-2.91	-3.15	-2.78
	Difference: -0.05 [-0.45; 0.35][5]		*Difference: -0.42 [-0.82; -0.02]*
Rate of hypoglycaemia (per patient year of exposure)			
Severe	0.02	0.02	0.02
Confirmed[4]	3.63	3.64	3.48
	Ratio: 1.10 [0.79; 1.52][6]		*Ratio: 1.03 [0.75; 1.40]*
Confirmed nocturnal[4]	0.56	0.63	0.75
	Ratio: 1.18 [0.66; 2.12][6]		*Ratio: 0.77 [0.44; 1.35]*

[1] Once-daily regimen (with main evening meal) + one or two of the following oral antidiabetes agents: SU, metformin or DPP-4 inhibitor.
[2] Flexible once-daily regimen (intervals of approximately 8-40 hours between doses) + one or two of the following oral antidiabetes agents SU, metformin or DPP-4 inhibitor.
[3] Once-daily regimen + one or two of the following oral antidiabetes agents: SU, metformin or DPP-4 inhibitor.
[4] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/l or by the patient needing third party assistance. Confirmed nocturnal hypoglycaemia was defined as episodes between midnight and 6 a.m.
[5] The difference is for Tresiba® Flex – Tresiba®
[6] The ratio is for Tresiba® Flex/Tresiba®.

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 $AUC_{GIR,0\text{-}12h,SS}$ and $AUC_{GIR,T,SS}$ 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 $AUC_{IDeg,T,SS}$ and $C_{max,\ IDeg,SS}$).

Gender
There is no gender difference in the pharmacokinetic properties of Tresiba®.

Elderly, race, 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 were investigated in children (6–11 years) and adolescents (12–18 years) and were comparable to those observed in adults with type 1 diabetes mellitus. Total exposure after a single dose is, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.

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.

Pharmaceutical particulars

List of excipients

Glycerol, metacresol, phenol, zinc acetate, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections.

Incompatibilities

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

Shelf life

After first opening, the product may be stored for a maximum of 8 weeks. Do not store above 30°C. Do not refrigerate.

Special precautions for storage

Before first use:
Store in a refrigerator (2°C – 8°C). Keep away from the freezing element.
Do not freeze.
Keep the cap on the pen in order to protect from light.

After first opening or carried as a spare:
Do not refrigerate. Do not store above 30°C.
Keep the cap on the pen in order to protect from light.
For storage conditions after first opening of the medicinal product, see *Shelf life*.

Nature and contents of container

3 ml solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.
Pack sizes of 1, 5 and multipack containing 10 (2 packs of 5) pre-filled pens.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling

The pre-filled pen (FlexTouch®) is designed to be used with NovoFine® or 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.
The pre-filled pen (FlexTouch®) is for use by one person only.
The pre-filled pen 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.
The patient should discard the needle after each injection.
Any waste material should be disposed of in accordance with local requirements.
For detailed instructions for use, see the package leaflet.

Marketing authorisation holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

novo nordisk®

8-9560-00-001-1

Instructions for the patient on how to use Tresiba® 100 units/ml solution for injection in pre-filled pen (FlexTouch®)

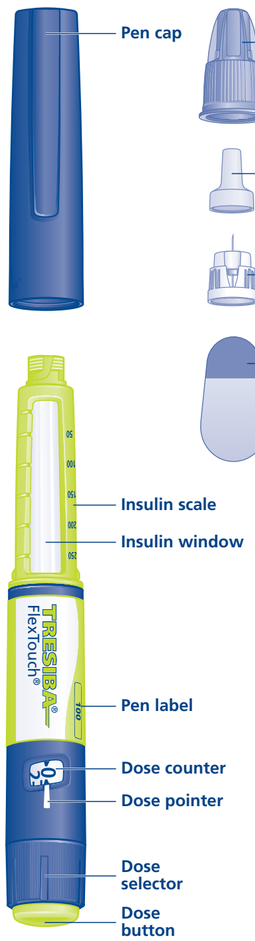
Please read these instructions carefully before using your FlexTouch® pre-filled pen.

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 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.
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 NovoTwist® disposable needles up to a length of 8 mm. Needles are not included in the pack.

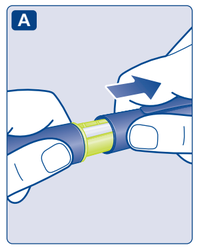
⚠ Important information
Pay special attention to these notes as they are important for safe use of the pen.

Tresiba® pre-filled pen and needle (example) (FlexTouch®)

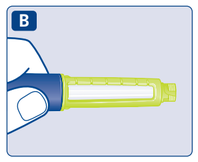


1 Prepare your pen

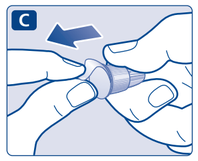
- **Check the name and strength on the label** of your pen, to make sure that it contains Tresiba® 100 units/ml. This is especially important if you take more than one type of insulin.
- **Pull off the pen cap.**



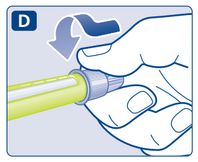
- **Check that the insulin in your pen is clear** and colourless.
Look through the insulin window. If the insulin looks cloudy, do not use the pen.



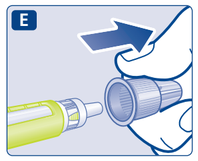
- **Take a new needle** and tear off the paper tab.



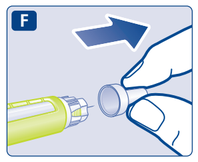
- **Push the needle straight onto the pen. Turn until it is on tight.**



- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.



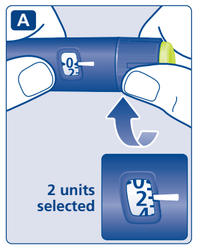
- **Pull off the inner needle cap and throw it away.**
If you try to put it back on, you may accidentally stick yourself with the needle.
A drop of insulin may appear at the needle tip. This is normal, but you must still check the insulin flow.



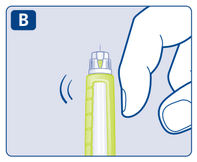
⚠ Always use a new needle for each injection.
This may prevent blocked needles, contamination, infection and inaccurate dosing.
⚠ Never use a bent or damaged needle.

2 Check the insulin flow

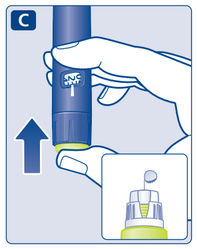
- **Always check the insulin flow before you start.**
This helps you to ensure that you get your full insulin dose.
- Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**



- 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.



- **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.

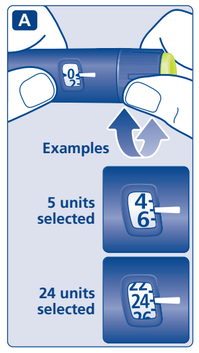


A small air bubble may remain at the needle tip, but it will not be injected.
If no drop appears, repeat steps 2**A** to 2**C** up to 6 times. If there is still no drop, change the needle and repeat steps 2**A** to 2**C** once more.
If a drop of insulin still does not appear, dispose of the pen and use a new one.

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

3 Select your dose

- **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.
The pen can dial up to a maximum of 80 units.

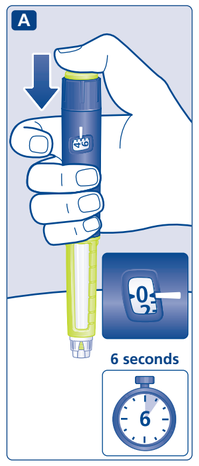


The dose selector changes the number of units. Only the dose counter and dose pointer will show how many units you select per dose.
You can select up to 80 units per dose. When your pen contains less than 80 units, the dose counter stops at the number of units left.
The dose selector clicks differently when turned forwards, backwards or past the number of units left. Do not count the pen clicks.

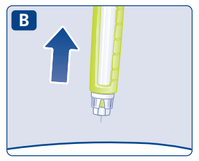
⚠ Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.
Do not count the pen clicks to select your dose.
Do not use the insulin scale, it only shows approximately how much insulin is left in your pen.

4 Inject your dose

- **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.



- **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.

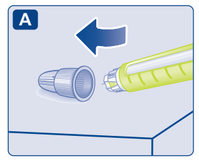


You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your dose.

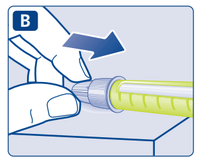
⚠ Always watch the dose counter to know how many units you inject.
The dose counter will show the exact number of units.
Do not count the pen clicks.

5 After your injection

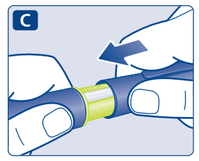
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully.



- **Put the pen cap on** your pen after each use to protect the insulin from light.



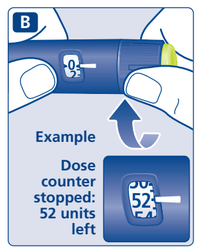
Always dispose of the needle after each injection to ensure convenient injections and prevent blocked needles. If the needle is blocked, you will **not** inject any insulin.
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

⚠ Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.
⚠ Always remove the needle from your pen after each injection.
This may prevent blocked needles, contamination, infection, leakage of insulin and inaccurate dosing.

6 How much insulin is left?

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

- **To see precisely how much insulin is left,** use the dose counter:
Turn the dose selector until the **dose counter stops.**
If it 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.



- 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 in doubt, take the full dose with a new pen.

⚠ 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.
- Caregivers must **be very careful when handling used needles** – to prevent needle injury and cross-infection.

Caring for your pen

- **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.