ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in pre-filled pen

2. 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 section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. (FlexTouch).

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

4.2 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 or in any combination with oral anti-diabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see section 5.1).

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 section 5.1). 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.

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

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 individually.

Special populations

Elderly patients (≥ 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 section 5.2).

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 section 5.2).

Paediatric population

Tresiba can be used in adolescents and children from the age of 1 year (see section 5.1). 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 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.

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).
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.
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 pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was 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 pioglitazone and Tresiba is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone 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.

4.5 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.

4.6 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 trimester. 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 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see section '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 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 section 5.1).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting. ATC code: A10AE06.

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).

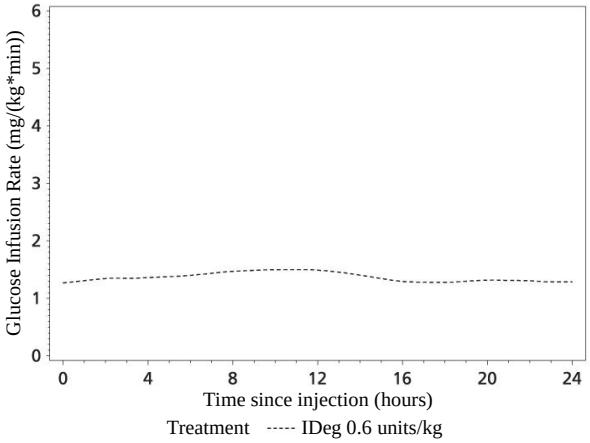

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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 ($AUC_{GIR,\tau,SS}$) and 2–24 hours ($AUC_{GIR2\text{-}24h,SS}$) as compared to insulin glargine, see Table 1.

Table 1 Day-to-day variability within-patients in glucose-lowering-effect of Tresiba and insulin glargine at steady-state in patients 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 ($AUC_{GIR,\tau,SS}$)	20	82
Day-to-day variability in glucose-lowering effect from 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$)	22	92

CV: within-patient 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 patients.

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 4275 patients to Tresiba (1102 in type 1 diabetes mellitus and 3173 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 patients ≥ 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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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**
HbA1c (%)			
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]*
Nocturnal confirmed[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. Nocturnal confirmed 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.

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target HbA_{1c} < 7.0% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator, estimated means) and body weight (-3.03 vs 0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Tresiba in:

- Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).

The efficacy and safety of Tresiba has been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). 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. Tresiba dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs 0.33), confirmed hypoglycaemia (57.71 vs 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs 7.60) were comparable with Tresiba versus insulin detemir. In both treatment arms, children aged 6-11 years had a numerically higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6-11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba versus insulin detemir, 0.68 and 1.09, respectively. No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus.

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

Gender

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

Elderly patients, 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 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

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.

6.3 Shelf life

30 months.

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

6.4 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 section 6.3.

6.5 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 (with or without needles), 5 (without needles) and multipack containing 10 (2 packs of 5) (without needles) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled pen (FlexTouch) 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.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/001
EU/1/12/807/002
EU/1/12/807/003
EU/1/12/807/004
EU/1/12/807/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

01/2015

Detailed information on this medicinal product is available on the web site of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 200 units/mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 200 units insulin degludec* (equivalent to 7.32 mg insulin degludec).

One pre-filled pen contains 600 units of insulin degludec in 3 mL solution.

*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. (FlexTouch).

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

4.2 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 or in any combination with oral anti-diabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see section 5.1).

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 section 5.1). 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.

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

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 individually.

Special populations

Elderly patients (≥ 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 section 5.2).

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 section 5.2).

Paediatric population

Tresiba can be used in adolescents and children from the age of 1 year (see section 5.1). 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 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 200 units/mL pre-filled pen delivers 2 – 160 units in steps of 2 units.

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).
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.

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 pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was 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 pioglitazone and Tresiba is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone 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.

4.5 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.

4.6 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 trimester. 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 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see section '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 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 section 5.1).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting. ATC code: A10AE06.

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).

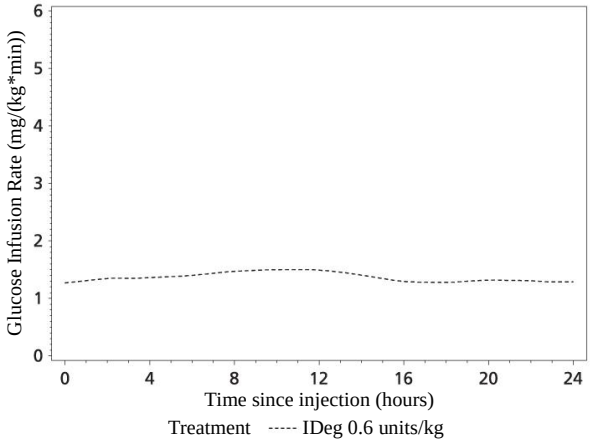

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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 ($AUC_{GIR,\tau,SS}$) and 2–24 hours ($AUC_{GIR2\text{-}24h,SS}$) as compared to insulin glargine, see Table 1.

Table 1 Day-to-day variability within-patients in glucose-lowering-effect of Tresiba and insulin glargine at steady-state in patients 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 ($AUC_{GIR,\tau,SS}$)	20	82
Day-to-day variability in glucose-lowering effect from 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$)	22	92

CV: within-patient 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 patients.

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 4275 patients to Tresiba (1102 in type 1 diabetes mellitus and 3173 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 patients ≥ 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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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**
HbA1c (%)			
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]*
Nocturnal confirmed[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. Nocturnal confirmed 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.

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target HbA_{1c} < 7.0% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator, estimated means) and body weight (-3.03 vs 0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Tresiba in:

- Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).

The efficacy and safety of Tresiba has been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). 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. Tresiba dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs 0.33), confirmed hypoglycaemia (57.71 vs 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs 7.60) were comparable with Tresiba versus insulin detemir. In both treatment arms, children aged 6-11 years had a numercally higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6-11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba versus insulin detemir, 0.68 and 1.09, respectively. No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent pateints with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus.

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

Gender

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

Elderly patients, 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 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

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.

6.3 Shelf life

30 months.

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

6.4 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 section 6.3.

6.5 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 (with or without needles), 2 (without needles), 3 (without needles) and multipack containing 6 (2 packs of 3) (without needles) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled pen (FlexTouch) 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.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/009
EU/1/12/807/006
EU/1/12/807/010
EU/1/12/807/012
EU/1/12/807/013
EU/1/12/807/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

01/2015

Detailed information on this medicinal product is available on the web site of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).

One cartridge 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 section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. (Penfill).

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

4.2 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 or in any combination with oral anti-diabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see section 5.1).

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.

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 section 5.1). 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.

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

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 individually.

Special populations

Elderly patients (≥ 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 section 5.2).

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 section 5.2).

Paediatric population

Tresiba can be used in adolescents and children from the age of 1 year (see section 5.1). 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 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 cartridge (Penfill) designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist injection needles.

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).
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.

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 pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was 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 pioglitazone and Tresiba is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone 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 Tresiba and 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.

4.5 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.

4.6 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 trimester. 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 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see section '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 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 section 5.1).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting. ATC code: A10AE06.

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 ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,total,SS} = 0.5$).

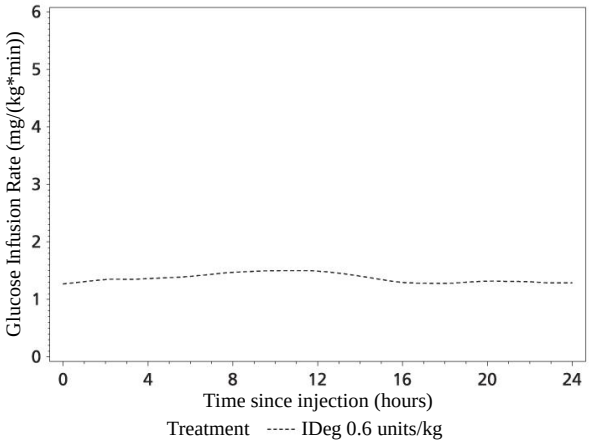

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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 ($AUC_{GIR,\tau,SS}$) and 2–24 hours ($AUC_{GIR2\text{-}24h,SS}$) as compared to insulin glargine, see Table 1.

Table 1 Day-to-day variability within-patients in glucose-lowering-effect of Tresiba and insulin glargine at steady-state in patients 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 ($AUC_{GIR,\tau,SS}$)	20	82
Day-to-day variability in glucose-lowering effect from 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$)	22	92

CV: within-patient 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.

There is no clinically relevant difference in the pharmacodynamics of Tresiba between elderly and younger adult patients.

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 4275 patients to Tresiba (1102 in type 1 diabetes mellitus and 3173 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 patients ≥ 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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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]*	
Nocturnal confirmed[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. Nocturnal confirmed 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**
HbA1c (%)			
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]*
Nocturnal confirmed[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. Nocturnal confirmed 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.

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target HbA_{1c} < 7.0% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator,

estimated means) and body weight (-3.03 vs 0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Tresiba in:

- Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).

The efficacy and safety of Tresiba has been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). 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. Tresiba dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs 0.33), confirmed hypoglycaemia (57.71 vs 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs 7.60) were comparable with Tresiba versus insulin detemir. In both treatment arms, children aged 6-11 years had a numercally higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6-11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba versus insulin detemir, 0.68 and 1.09, respectively. No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus.

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

Gender

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

Elderly patients, 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 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

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.

6.3 Shelf life

30 months.

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

6.4 Special precautions for storage

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

After first opening or carried as a spare:
Do not refrigerate. Do not store above 30°C.
Keep cartridges in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) in a carton.

Pack sizes of 5 and 10 cartridges.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridge (Penfill) 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.

The cartridge (Penfill) is for use by one person only. The cartridge 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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/007
EU/1/12/807/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

01/2015

Detailed information on this medicinal product is available on the web site of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

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

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSUR)**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
– At the request of the European Medicines Agency;
– Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch targeting all physicians and nurses who are expected to be involved in the treatment and management of diabetic patients and all pharmacists who are expected to dispense Tresiba.

The educational pack is aimed at increasing awareness about the introduction of a new strength of insulin in the European market and describing key differences in the design of the packages and the prefilled pen devices to minimise the risk of medication errors and mix up between the two different strengths of Tresiba.

The educational pack should contain:
– Direct Healthcare Professional Communication letter as described below;
– Summary of Product Characteristics and Package Leaflet;
– Poster for display in pharmacies/diabetic units;
– Patient Brochures.

The MAH shall ensure that healthcare professionals are informed that all patients who have been prescribed Tresiba should be provided with a patient brochure and be trained on the correct use of the prefilled pen before prescribing or dispensing Tresiba.

The Poster for pharmacies/diabetic units shall contain the following key elements:
– That Tresiba is available in 2 strengths;
– Key differences in the design of the packages and the prefilled pen devices;
– When prescribing to make sure that the correct strength is mentioned in the prescription slip;
– Always check the insulin label before dispensing to make sure the correct strength is delivered to the patient;
– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba ;
– Do not use outside of the prefilled pen device (e.g. syringes);
– Reporting of medication errors or any side effects.

The patient brochure shall contain the following key elements:
– That Tresiba is available in 2 strengths;
– Key differences in the design of the packages and the prefilled pen devices;
– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;
– Patients who are blind or have poor vision must be instructed always to get help/assistance from another person who has good vision and is trained in using the insulin device;
– Always use the dose recommended by your healthcare provider;
– Always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose;
– Check how many units were selected before injecting the insulin;
– The dose counter shows the number of units regardless of strength and no dose conversion should be done;
– Reporting of medication errors or any side effects.

The MAH shall agree the final text of the Direct Healthcare Professional Communication letter and the content of the patient brochure together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational pack in the Member State.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 300 units of insulin degludec in 3 mL solution
1 mL solution contains 100 units of insulin degludec (equivalent to 3.66 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

1 x 3 mL
1 x 3 mL + 7 NovoFine needles
1 x 3 mL + 7 NovoTwist needles
5 x 3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Needles are not included
Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/001 1 pen of 3 mL
EU/1/12/807/002 1 pen of 3 mL and 7 NovoFine needles
EU/1/12/807/003 1 pen of 3 mL and 7 NovoTwist needles
EU/1/12/807/004 5 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 100

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tresiba 100 units/mL solution for injection
insulin degludec
FlexTouch

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK LABEL (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 300 units of insulin degludec in 3 mL solution
1 mL solution contains 100 units of insulin degludec (equivalent to 3.66 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

Multipack: 10 (2 packs of 5) 3 mL pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/12/807/005 10 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 100

PARTICULARS TO APPEAR ON THE INNER PACKAGING

CARTON FOR MULTIPACK (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 300 units of insulin degludec in 3 mL solution
1 mL solution contains 100 units of insulin degludec (equivalent to 3.66 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

5 x 3 mL. Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/12/807/005 10 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 100

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (200 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 200 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 600 units of insulin degludec in 3 mL solution
1 mL solution contains 200 units of insulin degludec (equivalent to 7.32 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

1 x 3 mL
1 x 3 mL + 7 NovoFine needles
1 x 3 mL + 7 NovoTwist needles
2 x 3 mL
3 x 3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Needles are not included
Read the package leaflet before use
Subcutaneous use

Caution: One step equals 2 units
- the pen shows the dose

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution

Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/009 1 pen of 3 mL
EU/1/12/807/006 1 pen of 3 mL and 7 NovoFine needles
EU/1/12/807/010 1 pen of 3 mL and 7 NovoTwist needles
EU/1/12/807/012 2 pens of 3 mL
EU/1/12/807/013 3 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 200

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (200 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tresiba 200 units/mL solution for injection
insulin degludec
FlexTouch

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK LABEL (200 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 200 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 600 units of insulin degludec in 3 mL solution
1 mL solution contains 200 units of insulin degludec (equivalent to 7.32 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

Multipack: 6 (2 packs of 3) 3 mL pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

Caution: One step equals 2 units
- the pen shows the dose

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/12/807/015 6 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 200

PARTICULARS TO APPEAR ON THE INNER PACKAGING

CARTON FOR MULTIPACK (200 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 200 units/mL solution for injection in pre-filled pen
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One pre-filled pen contains 600 units of insulin degludec in 3 mL solution
1 mL solution contains 200 units of insulin degludec (equivalent to 7.32 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

3 x 3 mL. Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

Caution: One step equals 2 units
- the pen shows the dose

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP

After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/12/807/015 6 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba pre-filled pen 200

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (100 units/mL cartridge (Penfill))

1. NAME OF THE MEDICINAL PRODUCT

Tresiba 100 units/mL solution for injection in cartridge
insulin degludec

2. STATEMENT OF ACTIVE SUBSTANCE

One cartridge contains 300 units of insulin degludec in 3 mL solution
1 mL solution contains 100 units of insulin degludec (equivalent to 3.66 mg)

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (Penfill)

5 x 3 mL
10 x 3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
After first opening: Do not refrigerate. Do not store above 30°C. Keep the cartridge in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/807/007 5 cartridges of 3 mL
EU/1/12/807/008 10 cartridges of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tresiba cartridge 100

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (100 units/mL cartridge (Penfill))

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tresiba 100 units/mL solution for injection
insulin degludec
Penfill

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tresiba 100 units/mL solution for injection in pre-filled pen
insulin degludec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, pharmacist or nurse.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tresiba is and what it is used for

Tresiba is a long-acting basal insulin called insulin degludec. It is used to treat diabetes mellitus in adults, adolescents and children aged 1 year and above. Tresiba helps your body reduce your blood sugar level. It is used for once-daily dosing. On occasions when you cannot follow your regular dosing schedule you can change the time of dosing because Tresiba has a long blood-sugar-lowering effect (see section 3 for 'Flexibility in dosing time'). Tresiba can be used with meal-related rapid acting insulin products. In type 2 diabetes mellitus, Tresiba may be used in combination with tablets for diabetes or with injectable anti-diabetic products, other than insulin.
In type 1 diabetes mellitus, Tresiba must always be used in combination with meal-related rapid acting insulin products.

2. What you need to know before you use Tresiba

Do not use Tresiba
• if you are allergic to insulin degludec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tresiba. Be especially aware of the following:

• Low blood sugar (hypoglycaemia) – If your blood sugar is too low, follow the guidance for low blood sugar in section 4 'Possible side effects'.
• High blood sugar (hyperglycaemia) – If your blood sugar is too high, follow the guidance for high blood sugar in section 4 'Possible side effects'.
• Switching from other insulin products – The insulin dose may need to be changed if you switch from another type, brand or manufacturer of insulin. Talk to your doctor.

- Pioglitazone used together with insulin, see 'Pioglitazone' below.
- Eye disorder – Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder. If you experience eye problems talk to your doctor.
- Ensuring you use the right type of insulin – Always check the insulin label before each injection to avoid accidental mix-ups between different strengths of Tresiba as well as other insulin products.

If you have poor eyesight, please see section 3 'How to use Tresiba'.

Children and adolescents
Tresiba can be used in adolescents and children aged 1 year and above. There is no experience with the use of Tresiba in children below the age of 1 year.

Other medicines and Tresiba
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level – this may mean your insulin dose has to change.

Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- other medicines for diabetes (oral and injectable)
- sulphonamides – for infections
- anabolic steroids – such as testosterone
- beta-blockers – for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see section 4 'Warning signs of too low blood sugar')
- acetylsalicylic acid (and other salicylates) – for pain and mild fever
- monoamine oxidase (MAO) inhibitors – for depression
- angiotensin converting enzyme (ACE) inhibitors – for some heart problems or high blood pressure.

Your blood sugar level may rise (hyperglycaemia) if you take:
- danazol – for endometriosis
- oral contraceptives – birth control pills
- thyroid hormones – for thyroid problems
- growth hormone – for growth hormone deficiency
- glucocorticoids such as 'cortisone' – for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline – for asthma
- thiazides – for high blood pressure or if your body is keeping too much water (water retention).

Octreotide and lanreotide – used to treat a rare condition involving too much growth hormone (acromegaly). They may increase or decrease your blood sugar level.

Pioglitazone – oral anti-diabetic medicine used to treat type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke, who were treated with pioglitazone and insulin, experienced the development of heart failure. Inform your doctor immediately if you experience signs of heart failure such as unusual shortness of breath, rapid increase in weight or localised swelling (oedema).

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Tresiba with alcohol
If you drink alcohol, your need for insulin may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

Pregnancy and breast-feeding

It is not known if Tresiba affects the baby in pregnancy. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes is needed in pregnancy. Avoiding too low blood sugar (hypoglycaemia) is particularly important for the health of your baby.

Driving and using machines
Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This could be dangerous to yourself or others. Ask your doctor whether you can drive if:
- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients of Tresiba
Tresiba contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially 'sodium-free'.

3. How to use Tresiba

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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.

The pre-filled pen can provide a dose of 1-80 units in one injection in steps of 1 unit.

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.

Flexibility in dosing time
- Always follow your doctor's recommendation for dose.
- Use Tresiba once each day, preferably at the same time every day.
- On occasions when it is not possible to take Tresiba at the same time of the day, it can be taken at a different time of day. Make sure to have a minimum of 8 hours between the doses.
- 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.

When using other medicines, ask your doctor if your treatment needs to be adjusted.

Use in elderly patients (≥ 65 years old)
Tresiba can be used in elderly patients but 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.

Injecting your medicine
Before you use Tresiba for the first time, your doctor or nurse will show you how to use the pre-filled pen.

- Check the name and strength on the label of the pen to make sure it is Tresiba 100 units/mL.

Do not use Tresiba
- In insulin infusion pumps.
- If the pen is damaged or has not been stored correctly (see section 5 'How to store Tresiba').
- If the insulin does not appear clear and colourless.

How to inject
- 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 (see section 4).

Detailed instructions for use are provided on the other side of this leaflet.

If you use more Tresiba than you should
If you use too much insulin your blood sugar may get too low (hypoglycaemia), see advice in section 4 'Too low blood sugar'.

If you forget to use Tresiba
If you forget a dose, inject the missed dose when discovering the mistake, ensuring a minimum of 8 hours between doses. If you discover that you missed your previous dose when it is time to take your next regular scheduled dose, do not take a double dose, but resume your once-daily dosing schedule.

If you stop using Tresiba
Do not stop using your insulin without speaking to your doctor. If you stop using your insulin this could lead to a very high blood sugar level and ketoacidosis (a condition with too much acid in the blood), see advice in section 4 'Too high blood sugar'.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) may occur very commonly with insulin treatment (may affect more than 1 in 10 people). It can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level immediately. See advice in 'Too low blood sugar' below.

If you have a serious allergic reaction (seen rarely) to the insulin or any of the ingredients in Tresiba, stop using Tresiba and see a doctor straight away. The signs of a serious allergic reaction are:
- 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 rapid heartbeat or feeling dizzy.

Other side effects include:

Common *(may affect up to 1 in 10 people)*
Local reactions: Local reactions at the place you inject yourself may occur. The signs may include: pain, redness, hives, swelling and itching. The reactions usually disappear after a few days. See your

doctor if they do not disappear after a few weeks. Stop using Tresiba and see a doctor straight away if the reactions become serious. For more information see 'Serious allergic reaction' above.

Uncommon *(may affect up to 1 in 100 people)*
Skin changes where you use the injection (lipodystrophy): Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets from the pen.
Swelling around your joints: When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

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

General effects from diabetes treatment
- Too low blood sugar (hypoglycaemia)

Too low blood sugar may happen if you:
Drink alcohol; use too much insulin; exercise more than usual; eat too little or miss a meal.

Warning signs of too low blood sugar – these may come on suddenly:
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; short-lasting changes in your sight.

What to do if you get too low blood sugar
- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once, as with all basal insulin products improvement from the period of low blood sugar may be delayed.
- Wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on 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 passing out.

Let them know that if you pass out, they must:
- turn you on your side
- get medical help straight away
- **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 by someone who knows how to use it.
- If you are given glucagon you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even 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.

This is because the dosing or timing of your insulin injections, food or exercise may need to be changed.

- Too high blood sugar (hyperglycaemia)

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 of too high blood sugar – these normally appear gradually:
Flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more often, 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. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar
- Test your blood sugar level.
- Test your urine for ketones.
- Get medical help straight away.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tresiba

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the pen label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Before first use
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.

After first opening or if carried as a spare
Do not refrigerate. You can carry your Tresiba pre-filled pen (FlexTouch) with you and keep it at room temperature (not above 30°C) for up to 8 weeks.

Always keep the cap on the pen when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tresiba contains
- The active substance is insulin degludec. Each mL of solution contains 100 units (U) of insulin degludec. Each pre-filled pen (3 mL) contains 300 units (U) of insulin degludec.
- The other ingredients are glycerol, metacresol, phenol, zinc acetate, hydrochloric acid and

sodium hydroxide (for pH adjustment) and water for injections.

What Tresiba looks like and contents of the pack
Tresiba is presented as a clear and colourless solution for injection in pre-filled pen (300 units per 3 mL).

Pack sizes of 1 (with or without needles), 5 (without needles) and 10 (2 x 5) (without needles) pre-filled pens of 3 mL. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in 01/2015

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions 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 NovoTwist or NovoFine disposable needles up to a length of 8 mm.

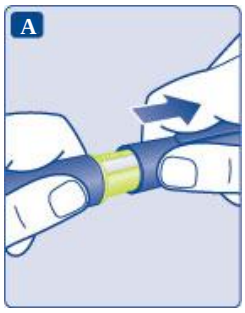
Important information
Pay special attention to these notes as they are important for safe use of the pen.

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

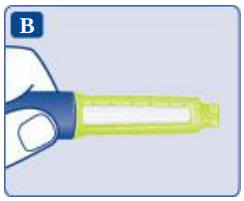
1 Prepare your pen

- **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.**



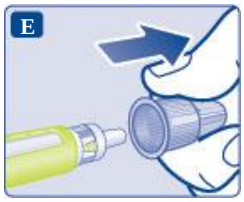
- **Check that the insulin in your pen is clear** and colourless.
  Look through the insulin window. If the insulin looks cloudy, do not use the pen.



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

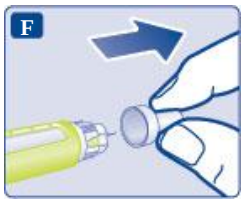
- **Push the needle straight onto the pen. Turn until it is on tight.**

- **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.



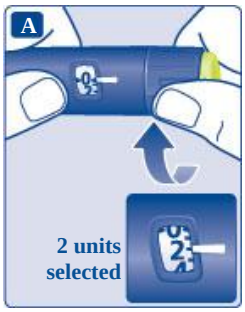
⚠ **Always use a new needle for each injection.**
This may prevent blocked needles, contamination, infection and inaccurate dosing.

⚠ **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.

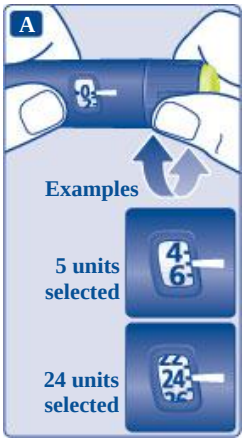
3 Select your dose

- **Make sure the dose counter shows 0 before you start.**
  The 0 lines 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

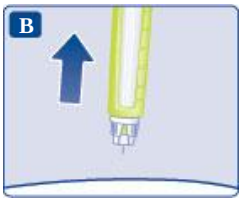
- **Insert the needle into your skin** as your doctor or nurse has shown you.

- **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.

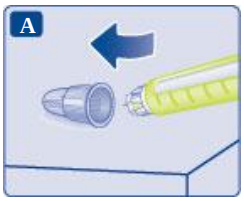


You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your dose.

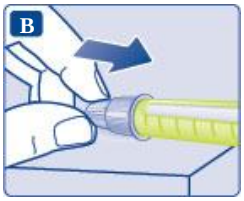
⚠ **Always watch the dose counter to know how many units you inject.**
The dose counter will show the exact number of units. Do not count the pen clicks.

5 After your injection

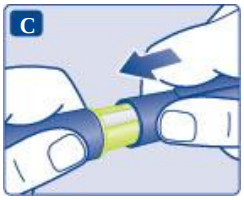
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- 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.

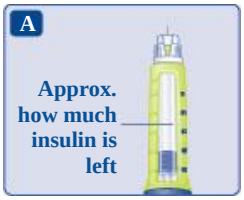
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

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

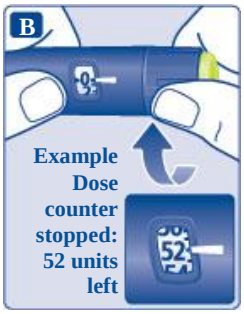
⚠ **Always remove the needle from your pen after each injection.**
This may prevent blocked needles, contamination, infection, leakage of insulin and inaccurate dosing.

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.

Package leaflet: Information for the patient

Tresiba 200 units/mL solution for injection in pre-filled pen
insulin degludec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, pharmacist or nurse.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tresiba is and what it is used for

Tresiba is a long-acting basal insulin called insulin degludec. It is used to treat diabetes mellitus in adults, adolescents and children aged 1 year and above. Tresiba helps your body reduce your blood sugar level. It is used for once-daily dosing. On occasions when you cannot follow your regular dosing schedule you can change the time of dosing because Tresiba has a long blood-sugar-lowering effect (see section 3 for 'Flexibility in dosing time').Tresiba can be used with meal-related rapid acting insulin products. In type 2 diabetes mellitus, Tresiba may be used in combination with tablets for diabetes or with injectable anti-diabetic products, other than insulin.
In type 1 diabetes mellitus, Tresiba must always be used in combination with meal-related rapid acting insulin products.

2. What you need to know before you use Tresiba

Do not use Tresiba
• if you are allergic to insulin degludec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tresiba. Be especially aware of the following:

• Low blood sugar (hypoglycaemia) – If your blood sugar is too low, follow the guidance for low blood sugar in section 4 'Possible side effects'.
• High blood sugar (hyperglycaemia) – If your blood sugar is too high, follow the guidance for high blood sugar in section 4 'Possible side effects'.
• Switching from other insulin products – The insulin dose may need to be changed if you switch from another type, brand or manufacturer of insulin. Talk to your doctor.

- Pioglitazone used together with insulin, see 'Pioglitazone' below.
- Eye disorder – Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder. If you experience eye problems talk to your doctor.
- Ensuring you use the right type of insulin – Always check the insulin label before each injection to avoid accidental mix-ups between different strengths of Tresiba as well as other insulin products.

If you have poor eyesight, please see section 3 'How to use Tresiba'.

Children and adolescents
Tresiba can be used in adolescents and children aged 1 year and above. There is no experience with the use of Tresiba in children below the age of 1 year.

Other medicines and Tresiba
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level – this may mean your insulin dose has to change.

Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- other medicines for diabetes (oral and injectable)
- sulphonamides – for infections
- anabolic steroids – such as testosterone
- beta-blockers – for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see section 4 'Warning signs of too low blood sugar')
- acetylsalicylic acid (and other salicylates) – for pain and mild fever
- monoamine oxidase (MAO) inhibitors – for depression
- angiotensin converting enzyme (ACE) inhibitors – for some heart problems or high blood pressure.

Your blood sugar level may rise (hyperglycaemia) if you take:
- danazol – for endometriosis
- oral contraceptives – birth control pills
- thyroid hormones – for thyroid problems
- growth hormone – for growth hormone deficiency
- glucocorticoids such as 'cortisone' – for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline – for asthma
- thiazides – for high blood pressure or if your body is keeping too much water (water retention).

Octreotide and lanreotide – used to treat a rare condition involving too much growth hormone (acromegaly). They may increase or decrease your blood sugar level.

Pioglitazone – oral anti-diabetic medicine used to treat type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke, who were treated with pioglitazone and insulin, experienced the development of heart failure. Inform your doctor immediately if you experience signs of heart failure such as unusual shortness of breath, rapid increase in weight or localised swelling (oedema).

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Tresiba with alcohol
If you drink alcohol, your need for insulin may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

Pregnancy and breast-feeding

It is not known if Tresiba affects the baby in pregnancy. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes is needed in pregnancy. Avoiding too low blood sugar (hypoglycaemia) is particularly important for the health of your baby.

Driving and using machines
Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This could be dangerous to yourself or others. Ask your doctor whether you can drive if:
- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients of Tresiba
Tresiba contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially 'sodium-free'.

3. How to use Tresiba

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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.

The pre-filled pen can provide a dose of 2-160 units in one injection in steps of 2 units.

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.

Flexibility in dosing time
- Always follow your doctor's recommendation for dose.
- Use Tresiba once each day, preferably at the same time every day.
- On occasions when it is not possible to take Tresiba at the same time of the day, it can be taken at a different time of day. Make sure to have a minimum of 8 hours between the doses.
- 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.

When using other medicines, ask your doctor if your treatment needs to be adjusted.

Use in elderly patients (≥ 65 years old)
Tresiba can be used in elderly patients but 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.

Injecting your medicine
Before you use Tresiba for the first time, your doctor or nurse will show you how to use the pre-filled pen.

- Check the name and strength on the label of the pen to make sure it is Tresiba 200 units/mL.
- The dose counter of your pen shows the exact number of insulin units. Do not make any dose re-calculation.

Do not use Tresiba
- In insulin infusion pumps.
- If the pen is damaged or has not been stored correctly (see section 5 'How to store Tresiba').
- If the insulin does not appear clear and colourless.

How to inject
- 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 (see section 4).

Detailed instructions for use are provided on the other side of this leaflet.

If you use more Tresiba than you should
If you use too much insulin your blood sugar may get too low (hypoglycaemia), see advice in section 4 'Too low blood sugar'.

If you forget to use Tresiba
If you forget a dose, inject the missed dose when discovering the mistake, ensuring a minimum of 8 hours between doses. If you discover that you missed your previous dose when it is time to take your next regular scheduled dose, do not take a double dose, but resume your once-daily dosing schedule.

If you stop using Tresiba
Do not stop using your insulin without speaking to your doctor. If you stop using your insulin this could lead to a very high blood sugar level and ketoacidosis (a condition with too much acid in the blood), see advice in section 4 'Too high blood sugar'.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) may occur very commonly with insulin treatment (may affect more than 1 in 10 people). It can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level immediately. See advice in 'Too low blood sugar' below.

If you have a serious allergic reaction (seen rarely) to the insulin or any of the ingredients in Tresiba, stop using Tresiba and see a doctor straight away. The signs of a serious allergic reaction are:
- 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 rapid heartbeat or feeling dizzy.

Other side effects include:

Common *(may affect up to 1 in 10 people)*

Local reactions: Local reactions at the place you inject yourself may occur. The signs may include: pain, redness, hives, swelling and itching. The reactions usually disappear after a few days. See your doctor if they do not disappear after a few weeks. Stop using Tresiba and see a doctor straight away if the reactions become serious. For more information see 'Serious allergic reaction' above.

Uncommon *(may affect up to 1 in 100 people)*
Skin changes where you use the injection (lipodystrophy): Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets from the pen.
Swelling around your joints: When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

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

General effects from diabetes treatment
- Too low blood sugar (hypoglycaemia)

Too low blood sugar may happen if you:
Drink alcohol; use too much insulin; exercise more than usual; eat too little or miss a meal.

Warning signs of too low blood sugar – these may come on suddenly:
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; short-lasting changes in your sight.

What to do if you get too low blood sugar
- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once, as with all basal insulin products improvement from the period of low blood sugar may be delayed.
- Wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on 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 passing out.

Let them know that if you pass out, they must:
- turn you on your side
- get medical help straight away
- **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 by someone who knows how to use it.
- If you are given glucagon you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even 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.

This is because the dosing or timing of your insulin injections, food or exercise may need to be changed.

- Too high blood sugar (hyperglycaemia)

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 of too high blood sugar – these normally appear gradually:
Flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more often, 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. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar
- Test your blood sugar level.
- Test your urine for ketones.
- Get medical help straight away.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tresiba

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the pen label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Before first use
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.

After first opening or if carried as a spare
Do not refrigerate. You can carry your Tresiba pre-filled pen (FlexTouch) with you and keep it at room temperature (not above 30°C) for up to 8 weeks.

Always keep the cap on the pen when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tresiba contains
- The active substance is insulin degludec. Each mL of solution contains 200 units (U) of insulin

degludec. Each pre-filled pen (3 mL) contains 600 units (U) of insulin degludec.

- The other ingredients are glycerol, metacresol, phenol, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

What Tresiba looks like and contents of the pack
Tresiba is presented as a clear and colourless solution for injection in pre-filled pen (600 units per 3 mL).

Pack sizes of 1 (with or without needles), 2 (without needles), 3 (without needles) and 6 (2 x 3) (without needles) pre-filled pens of 3 mL. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in 01/2015

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions on how to use Tresiba 200 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 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.

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 NovoTwist or NovoFine disposable needles up to a length of 8 mm.

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

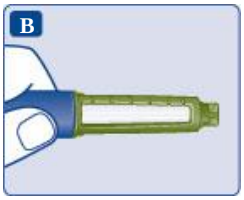
Tresiba pre-filled pen and needle (example) (FlexTouch)

1 Prepare your pen

- **Check the name and strength on the label** of your pen, to make sure that it contains Tresiba 200 units/mL. This is especially important if you take more than one type of insulin.

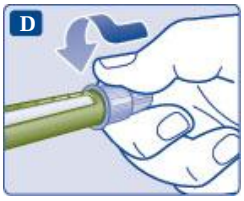
- **Pull off the pen cap.**

- **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.

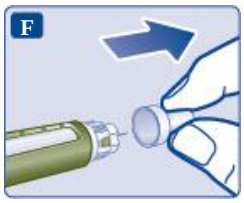
- **Push the needle straight onto the pen. Turn until it is on tight.**



- **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

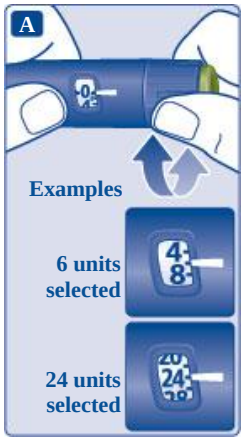
- **Make sure the dose counter shows 0 before you start.**
  The 0 lines up with the dose pointer.

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

- The dose counter shows the dose dialled in units. **Do not make any dose re-calculation.**

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 160 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 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 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

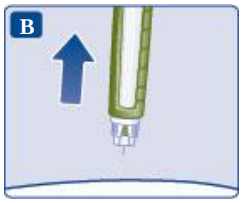
- **Insert the needle into your skin** as your doctor or nurse has shown you.

- **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.

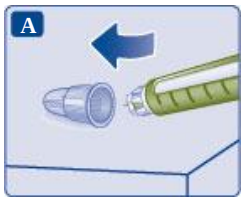


You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your dose.

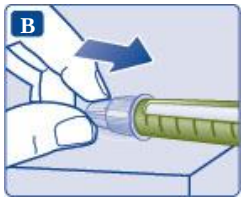
⚠ **Always watch the dose counter to know how many units you inject.**
The dose counter will show the exact number of units. Do not count the pen clicks.

5 After your injection

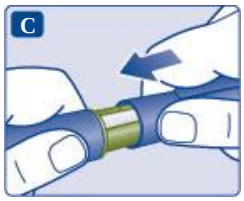
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- 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.

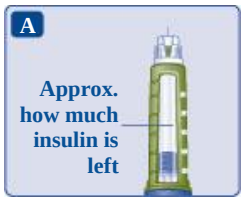
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

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

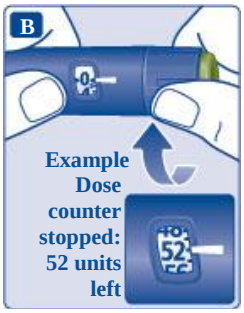
⚠ **Always remove the needle from your pen after each injection.**
This may prevent blocked needles, contamination, infection, leakage of insulin and inaccurate dosing.

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 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.



- 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.

Package leaflet: Information for the patient

Tresiba 100 units/mL solution for injection in cartridge
insulin degludec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, pharmacist or nurse.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tresiba is and what it is used for

Tresiba is a long-acting basal insulin called insulin degludec. It is used to treat diabetes mellitus in adults, adolescents and children aged 1 year and above. Tresiba helps your body reduce your blood sugar level. It is used for once-daily dosing. On occasions when you cannot follow your regular dosing schedule you can change the time of dosing because Tresiba has a long blood-sugar-lowering effect (see section 3 for 'Flexibility in dosing time'). Tresiba can be used with meal-related rapid acting insulin products. In type 2 diabetes mellitus, Tresiba may be used in combination with tablets for diabetes or with injectable anti-diabetic products, other than insulin.
In type 1 diabetes mellitus, Tresiba must always be used in combination with meal-related rapid acting insulin products.

2. What you need to know before you use Tresiba

Do not use Tresiba
• if you are allergic to insulin degludec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tresiba. Be especially aware of the following:

• Low blood sugar (hypoglycaemia) – If your blood sugar is too low, follow the guidance for low blood sugar in section 4 'Possible side effects'.
• High blood sugar (hyperglycaemia) – If your blood sugar is too high, follow the guidance for high blood sugar in section 4 'Possible side effects'.
• Switching from other insulin products – The insulin dose may need to be changed if you switch from another type, brand or manufacturer of insulin. Talk to your doctor.

- Pioglitazone used together with insulin, see 'Pioglitazone' below.
- Eye disorder – Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder. If you experience eye problems talk to your doctor.
- Ensuring you use the right type of insulin – Always check the insulin label before each injection to avoid accidental mix-ups between Tresiba and other insulin products.

If you have poor eyesight, please see section 3 'How to use Tresiba'.

Children and adolescents
Tresiba can be used in adolescents and children aged 1 year and above. There is no experience with the use of Tresiba in children below the age of 1 year.

Other medicines and Tresiba
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level – this may mean your insulin dose has to change.

Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- other medicines for diabetes (oral and injectable)
- sulphonamides – for infections
- anabolic steroids – such as testosterone
- beta-blockers – for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see section 4 'Warning signs of too low blood sugar')
- acetylsalicylic acid (and other salicylates) – for pain and mild fever
- monoamine oxidase (MAO) inhibitors – for depression
- angiotensin converting enzyme (ACE) inhibitors – for some heart problems or high blood pressure.

Your blood sugar level may rise (hyperglycaemia) if you take:
- danazol – for endometriosis
- oral contraceptives – birth control pills
- thyroid hormones – for thyroid problems
- growth hormone – for growth hormone deficiency
- glucocorticoids such as 'cortisone' – for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline – for asthma
- thiazides – for high blood pressure or if your body is keeping too much water (water retention).

Octreotide and lanreotide – used to treat a rare condition involving too much growth hormone (acromegaly). They may increase or decrease your blood sugar level.

Pioglitazone – oral anti-diabetic medicine used to treat type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke, who were treated with pioglitazone and insulin, experienced the development of heart failure. Inform your doctor immediately if you experience signs of heart failure such as unusual shortness of breath, rapid increase in weight or localised swelling (oedema).

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Tresiba with alcohol
If you drink alcohol, your need for insulin may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

Pregnancy and breast-feeding
It is not known if Tresiba affects the baby in pregnancy. If you are pregnant or breast-feeding, think

you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes is needed in pregnancy. Avoiding too low blood sugar (hypoglycaemia) is particularly important for the health of your baby.

Driving and using machines
Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This could be dangerous to yourself or others. Ask your doctor whether you can drive if:
- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients of Tresiba
Tresiba contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially 'sodium-free'.

3. How to use Tresiba

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

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.

Flexibility in dosing time
- Always follow your doctor's recommendation for dose.
- Use Tresiba once each day, preferably at the same time every day.
- On occasions when it is not possible to take Tresiba at the same time of the day, it can be taken at a different time of day. Make sure to have a minimum of 8 hours between the doses.
- 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.

When using other medicines, ask your doctor if your treatment needs to be adjusted.

Use in elderly patients (≥ 65 years old)
Tresiba can be used in elderly patients but 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.

Injecting your medicine
Before you use Tresiba for the first time, your doctor or nurse will show you how to use it.
- Please also read the manual that comes with your insulin delivery system.
- Check the name and strength on the label to make sure it is Tresiba 100 units/mL.

Do not use Tresiba
- In insulin infusion pumps.

- If the cartridge or the delivery system you are using is damaged. Take it back to your supplier. See your delivery system manual for further instructions.
- If the cartridge is damaged or has not been stored correctly (see section 5 'How to store Tresiba').
- If the insulin does not appear clear and colourless.

How to inject
- 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 (see section 4).

If you use more Tresiba than you should
If you use too much insulin your blood sugar may get too low (hypoglycaemia), see advice in section 4 'Too low blood sugar'.

If you forget to use Tresiba
If you forget a dose, inject the missed dose when discovering the mistake, ensuring a minimum of 8 hours between doses. If you discover that you missed your previous dose when it is time to take your next regular scheduled dose, do not take a double dose, but resume your once-daily dosing schedule.

If you stop using Tresiba
Do not stop using your insulin without speaking to your doctor. If you stop using your insulin this could lead to a very high blood sugar level and ketoacidosis (a condition with too much acid in the blood), see advice in section 4 'Too high blood sugar'.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) may occur very commonly with insulin treatment (may affect more than 1 in 10 people). It can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level immediately. See advice in 'Too low blood sugar' below.

If you have a serious allergic reaction (seen rarely) to the insulin or any of the ingredients in Tresiba, stop using Tresiba and see a doctor straight away. The signs of a serious allergic reaction are:
- 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 rapid heartbeat or feeling dizzy.

Other side effects include:

Common *(may affect up to 1 in 10 people)*
Local reactions: Local reactions at the place you inject yourself may occur. The signs may include: pain, redness, hives, swelling and itching. The reactions usually disappear after a few days. See your doctor if they do not disappear after a few weeks. Stop using Tresiba and see a doctor straight away if the reactions become serious. For more information see 'Serious allergic reaction' above.

Uncommon *(may affect up to 1 in 100 people)*
Skin changes where you use the injection (lipodystrophy): Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets.
Swelling around your joints: When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

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

General effects from diabetes treatment
- Too low blood sugar (hypoglycaemia)

Too low blood sugar may happen if you:
Drink alcohol; use too much insulin; exercise more than usual; eat too little or miss a meal.

Warning signs of too low blood sugar – these may come on suddenly:
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; short-lasting changes in your sight.

What to do if you get too low blood sugar
- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once, as with all basal insulin products improvement from the period of low blood sugar may be delayed.
- Wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on 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 passing out.

Let them know that if you pass out, they must:
- turn you on your side
- get medical help straight away
- **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 by someone who knows how to use it.
- If you are given glucagon you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even 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.

This is because the dosing or timing of your insulin injections, food or exercise may need to be changed.

- Too high blood sugar (hyperglycaemia)

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 of too high blood sugar – these normally appear gradually:
Flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more often, 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. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar
- Test your blood sugar level.
- Test your urine for ketones.
- Get medical help straight away.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tresiba

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the Penfill label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Before first use
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
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.

Always keep Tresiba Penfill in the outer carton when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tresiba contains
- The active substance is insulin degludec. Each mL of solution contains 100 units (U) of insulin degludec. Each cartridge (3 mL) contains 300 units (U) of insulin degludec.
- The other ingredients are glycerol, metacresol, phenol, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

What Tresiba looks like and contents of the pack

Tresiba is presented as a clear and colourless solution for injection in a cartridge (300 units per 3 mL).

Pack sizes of 5 and 10 cartridges of 3 mL. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in 01/2015

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Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu