SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tresiba 100 units/mL solution for injection in pre-filled pen
One pre-filled pen contains 300 units of insulin degludec in 3 mL solution.
1 mL solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tresiba 100 units/mL solution for injection in pre-filled pen
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
This medicinal product 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. One (1) unit of insulin degludec corresponds to 1 international unit of human insulin, 1 unit of insulin glargine (100 units/mL), or 1 unit of insulin detemir.

In patients with type 2 diabetes mellitus, this medicinal product can be administered alone or in any combination with oral antidiabetic 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.

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 solution for injection in a pre-filled pen
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 the medicinal product.
- 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. There is no clinical experience with flexibility in dosing time of Tresiba in children and adolescents.

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 mealtime 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 antidiabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus
For patients with type 2 diabetes taking once-daily 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.

A dose reduction of 20% based on the previous basal insulin dose followed by individual dosage adjustments should be considered when
- transferring to Tresiba from twice-daily basal insulin
- transferring to Tresiba from insulin glargine (300 units/mL)

Patients with type 1 diabetes mellitus
For patients with type 1 diabetes a dose reduction of 20% based on the previous basal insulin dose or basal component of a continuous subcutaneous insulin infusion regimen should be considered with subsequent individual dosage adjustments 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 (≥65 years old)
Tresiba can be used in elderly. 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
There is no clinical experience with the use of this medicinal product in children below the age of 1 year. This medicinal product 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
Subcutaneous use only.

Tresiba must not be administered intravenously as it may result in severe hypoglycaemia.
This medicinal product must not be administered intramuscularly as it may change the absorption.
This medicinal product must not be used in insulin infusion pumps.
Tresiba must not be drawn from the cartridge of the pre-filled pen into a syringe (see section 4.4).

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

Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see section 6.6).

Tresiba 100 units/mL and Tresiba 200 units/mL solution for injection in a pre-filled pen
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.
– The 200 units/mL pre-filled pen delivers 2–160 units in steps of 2 units.

Tresiba 100 units/mL solution for injection in a cartridge
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.

Skin and subcutaneous tissue disorders
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

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.

To avoid dosing errors and potential overdose, patients and healthcare professionals should never use a syringe to draw the medicinal product from the cartridge in the pre-filled pen.
In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see section 6.6).

Insulin antibodies

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

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
The use of Tresiba in pregnant women with diabetes has been investigated in an interventional trial (see section 5.1). A moderate amount of clinical trial and post-marketing data in pregnant women (more than 400 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.

The treatment with Tresiba may be considered during pregnancy, if clinically needed.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements usually return rapidly to pre-pregnancy values. Careful monitoring of glucose control is recommended and the insulin dose adjusted on an individual basis.

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

This medicinal product has no or negligible influence on the ability to drive and use machines. However, 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	Adverse reaction
Immune system disorders	Rare	Hypersensitivity Urticaria
Metabolism and nutrition disorders	Very common	Hypoglycaemia
Skin and subcutaneous tissue disorders	Uncommon	Lipodystrophy
	Not known	Cutaneous amyloidosis†
General disorders and administration site conditions	Common	Injection site reactions
	Uncommon	Peripheral oedema

† ADR from postmarketing sources.

Description of selected adverse reactions

Immune system disorders

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

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

Hypoglycaemia

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

Skin and subcutaneous tissue disorders

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

Injection site reactions

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

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 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

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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).

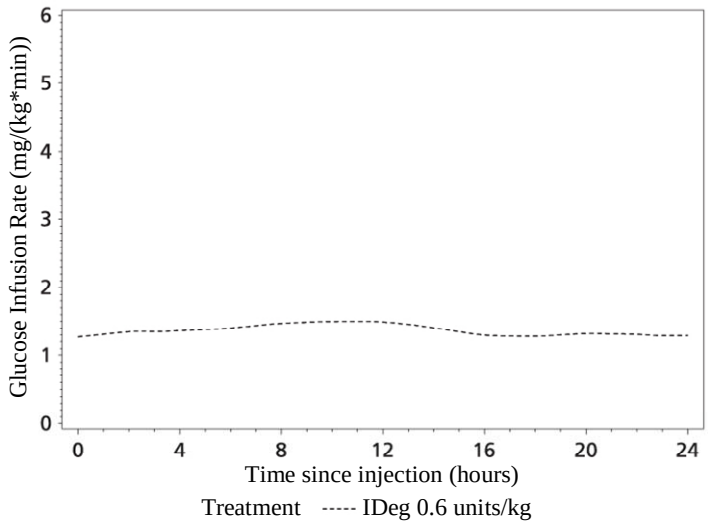


Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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 day-to-day variability, expressed as the coefficient of variation, in glucose-lowering effect during one dosing interval of 0-24 hours at steady state ($AUC_{GIR,\tau,SS}$) is 20% for insulin degludec, which is significantly lower than for insulin glargine (100 units/mL).

The total glucose-lowering effect of Tresiba increases linearly with increasing doses.

The total glucose-lowering effect is comparable for Tresiba 100 units/mL and 200 units/mL after administration of the same doses of the two products.

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

Clinical efficacy and safety

11 multinational clinical trials of 26 or 52 weeks' duration were conducted as controlled, open-label, randomised, parallel, treat-to-target trials exposing 4,275 patients to Tresiba (1,102 in type 1 diabetes mellitus and 3,173 in type 2 diabetes mellitus).

In the open-label trials the effect of Tresiba was tested in patients with type 1 diabetes mellitus (Table 2), in insulin naïve patients (insulin initiation in type 2 diabetes mellitus, Table 3) and in previous insulin users (insulin intensification in type 2 diabetes mellitus, Table 4) with fixed as well as flexible dosing time (Table 5), 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 (100 units/mL)). 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 4).

In a prospectively planned meta-analysis across seven open-label 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 1) and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine (100 units/ml) (administered according to label). The reduction in hypoglycaemia was achieved at a lower average FPG level with Tresiba than with insulin glargine.

Table 1 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 2 Results from open-label clinical trials in type 1 diabetes mellitus

	52 weeks of treatment		26 weeks of treatment	
	Tresiba[1]	**Insulin glargine (100 units/mL)**[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 3 Results from open-label clinical trials in insulin naïve type 2 diabetes mellitus (insulin initiation)

	52 weeks of treatment		26 weeks of treatment	
	Tresiba[1]	**Insulin glargine (100 units/mL)**[1]	**Tresiba**[1]	**Insulin glargine (100 units/mL)**[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 4 Results from open-label 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 (100 units/mL)[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 5 Results from an open-label clinical trial with flexible dosing of Tresiba in type 2 diabetes mellitus

	26 weeks of treatment		
	Tresiba[1]	**Tresiba Flex[2]**	**Insulin glargine (100 units/mL)[3]**
N	**228**	**229**	**230**
HbA_{1c} (%)			
End of trial	7.3	7.2	7.1
Mean change	-1.07	-1.28	-1.26
	Difference: -0.13 [-0.29; 0.03][5]	*Difference: 0.04 [-0.12; 0.20]*	
FPG (mmol/L)			
End of trial	5.8	5.8	6.2
Mean change from baseline	-2.91	-3.15	-2.78

	Difference: -0.05 [-0.45; 0.35][5]	*Difference: -0.42 [-0.82; -0.02]*	
Rate of hypoglycaemia (per patient year of exposure)			
Severe	0.02	0.02	0.02
Confirmed[4]	3.63	3.64	3.48
	Ratio: 1.10 [0.79; 1.52][6]	*Ratio: 1.03 [0.75; 1.40]*	
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).

Furthermore, two 64-week controlled, double-blind, randomised, cross-over, treat-to-target trials were conducted in patients with at least one risk factor for hypoglycaemia and with type 1 diabetes mellitus (501 patients) or type 2 diabetes mellitus (721 patients). Patients were randomised to either Tresiba or insulin glargine (100 units/mL) followed by cross-over. The trials evaluated the rate of hypoglycaemia upon treatment with Tresiba compared to insulin glargine (100 units/mL) (see Table 6).

Table 6 Results from the double-blind, cross-over clinical trials in type 1 and type 2 diabetes mellitus

	Type 1 diabetes mellitus		**Type 2 diabetes mellitus**	
	Tresiba[1]	**Insulin glargine (100 units/mL)[1]**	**Tresiba[2]**	**Insulin glargine (100 units/mL)[2]**
N	**501**		**721**	
HbA_{1c} (%)				
Baseline	7.6		7.6	

End of treatment	6.9	6.9	7.1	7.0
FPG (mmol/L)				
Baseline	9.4		7.6	
End of treatment	7.5	8.4	6.0	6.1
Rate of severe hypoglycaemia[3]				
Maintenance period[4]	0.69	0.92	0.05	0.09
	Ratio: 0.65 [0.48; 0.89]		*Ratio: 0.54 [0.21; 1.42]*	
Rate of severe or BG confirmed symptomatic hypoglycaemia[3,5]				
Maintenance period[4]	22.01	24.63	1.86	2.65
	Ratio: 0.89 [0.85; 0.94]		*Ratio: 0.70 [0.61; 0.80]*	
Rate of severe or BG confirmed symptomatic nocturnal hypoglycaemia[3.5]				
Maintenance period[4]	2.77	4.29	0.55	0.94
	Ratio: 0.64 [0.56; 0.73]		*Ratio: 0.58 [0.46; 0.74]*	

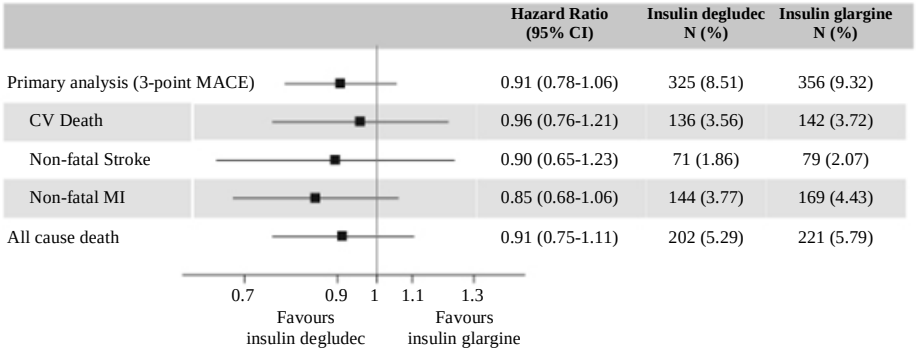
[1] In a once-daily regimen + insulin aspart to cover mealtime insulin requirements
[2] In a once-daily regimen ± OADs (any combination of metformin, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, thiazolidinediones, and sodium glucose cotransporter-2 inhibitor)
[3] Per patient year of exposure
[4] Episodes from week 16 in each treatment period
[5] Blood glucose (BG) confirmed symptomatic hypoglycaemia was defined as episodes confirmed by a plasma glucose value of less than 3.1 mmol/L, with symptoms consistent with hypoglycaemia. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Cardiovascular evaluation

DEVOTE was a randomised, double-blind, and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of Tresiba versus insulin glargine (100 units/mL) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events.

The primary analysis was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was designed as a non-inferiority trial to exclude a pre-specified risk margin of 1.3 for the hazard ratio (HR) of MACE comparing Tresiba to insulin glargine. The cardiovascular safety of Tresiba as compared to insulin glargine was confirmed (HR 0.91 [0.78; 1.06]) (Figure 2).

Results from subgroup analyses (e.g. sex, diabetes duration, CV risk group and previous insulin regimen) was aligned with the primary analysis.



N: Number of subjects with a first EAC confirmed event during trial. %: Percentage of subjects with a first EAC confirmed event relative to the number of randomised subjects. EAC: Event adjudication committee. CV: Cardiovascular. MI: Myocardial infarction. CI: 95% confidence interval.

Figure 2 Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE

At baseline, HbA_{1c} was 8.4% in both treatment groups and after 2 years HbA_{1c} was 7.5% both with Tresiba and insulin glargine.
Tresiba was superior compared to insulin glargine in terms of a lower rate of severe hypoglycaemic events and a lower proportion of subjects experiencing severe hypoglycaemia. The rate of nocturnal severe hypoglycaemia was significantly lower for Tresiba compared to insulin glargine (Table 7).

Table 7 Results from DEVOTE

	Tresiba[1]	**Insulin glargine (100 units/mL)**[1]
N	3,818	3,819
Rate of hypoglycaemia (per 100 patient years of observation)		
Severe	3.70	6.25
	Rate ratio: 0.60 [0.48; 0.76]	
Nocturnal severe[2]	0.65	1.40
	Rate ratio: 0.47 [0.31; 0.73]	
Proportions of patients with hypoglycaemia (percent of patients)		
Severe	4.9	6.6
	Odds ratio: 0.73 [0.60; 0.89]	

[1] In addition to standard of care for diabetes and cardiovascular disease
[2] Nocturnal severe hypoglycaemia was defined as episodes between midnight and 6 a.m.

Pregnancy
Tresiba has been studied in an open-label, randomised, active controlled clinical trial, in which pregnant women with type 1 diabetes mellitus were treated within a basal-bolus treatment regimen with Tresiba (92 women) or insulin detemir (96 women) as basal insulin, both in combination with insulin aspart as meal time insulin (EXPECT).

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

No clinically relevant differences were observed between Tresiba and insulin detemir for the maternal safety endpoints (hypoglycaemia, pre-term delivery, pre-eclampsia, non-planned caesarean section and adverse events during the pregnancy). The majority of the adverse events reported in both groups were non-serious, mild in severity, unlikely related to the trial product and had the outcome "recovered/resolved". No deaths were reported in the subjects who were randomised in the trial.

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

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 have 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 $AUC_{IDeg,0\text{-}12h,SS}$ and $AUC_{IDeg,\tau,SS}$ 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 this medicinal product.

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

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

5.3 Preclinical safety data

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Metacresol
Phenol
Zinc acetate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with any other medicinal products.

Substances added to Tresiba may cause degradation of insulin degludec.

Tresiba must not be added to infusion fluids.

6.3 Shelf life

30 months.

Tresiba 100 units/mL solution for injection in pre-filled pen
After first opening or carried as a spare, the medicinal product may be stored for a maximum of 8 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C). Keep the cap on the pen in order to protect from light.

6.4 Special precautions for storage

Tresiba 100 units/mL solution for injection in pre-filled pen
Before first use:
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep away from the freezing element.
Keep the cap on the pen in order to protect it from light.

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

6.5 Nature and contents of container

Tresiba 100 units/mL solution for injection in pre-filled pen
3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (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

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

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

Tresiba which has been frozen must not be used.

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

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

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

For detailed instructions for use, see the package leaflet.

Tresiba in a pre-filled pen is available in two strengths. “Tresiba 100 units/mL” or “Tresiba 200 units/mL” is clearly marked on the pen label and packaging.

Tresiba 100 units/mL solution for injection in pre-filled pen
Tresiba 100 units/mL packaging and label are light green.
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.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04668/0410

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

13/01/2022