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:

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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

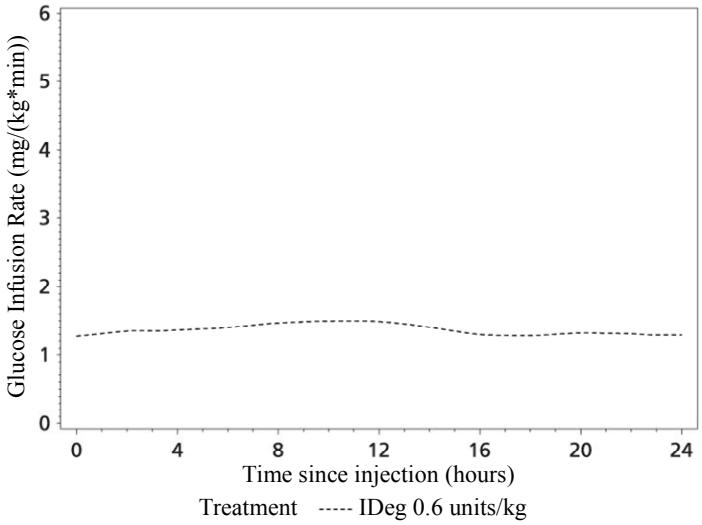

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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. Can be stored in a refrigerator (2°C – 8°C).

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 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.

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

04/2015

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:

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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

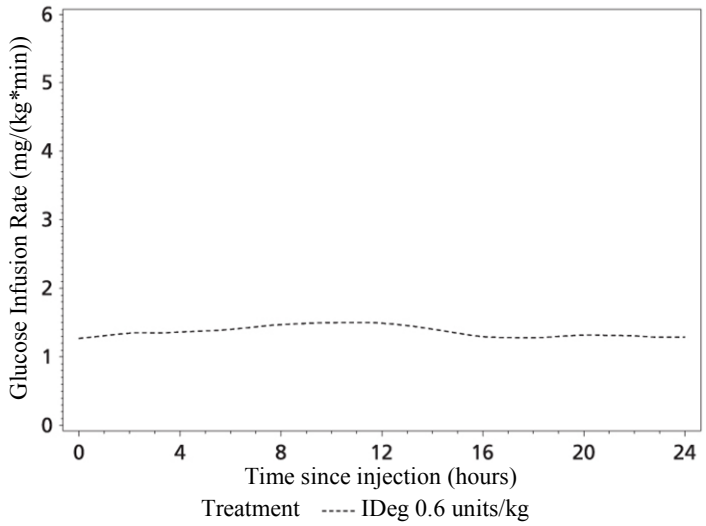

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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. Can be stored in a refrigerator (2°C – 8°C).

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 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.

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

04/2015

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

Ireland

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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

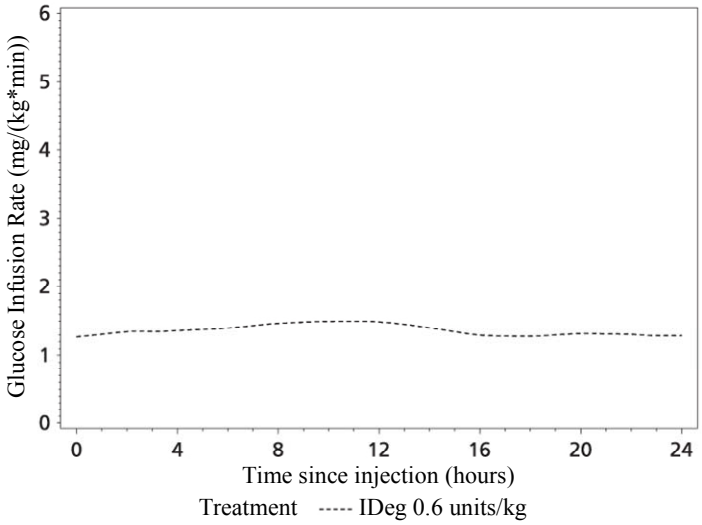

Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

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

04/2015

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