Regulatory Operations

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LIFT - Current 1

ROW
Patient/Professional

Colour: PMS 280C +
PMS 382C

Tresiba®
FlexTouch®

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

Qualitative and quantitative composition
1 ml solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).
One pre-filled pen contains 300 units of insulin degludec in 3 ml solution.
*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see *List of excipients.*

Pharmaceutical form
Solution for injection.
Clear, colourless, neutral solution.

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

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 (100 units/ml) or 1 unit of insulin detemir.

In patients with type 2 diabetes mellitus, Tresiba® can be administered alone or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see *Pharmacodynamic properties*).

In type 1 diabetes mellitus, Tresiba® must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.
Tresiba® is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose (FPG).
As with all insulin products, adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Tresiba® 100 units/ml and Tresiba® 200 units/ml
Tresiba® is available in two strengths. For both, the needed dose is dialled in units. The dose steps, however, differ between the two strengths of Tresiba®.
With Tresiba® 100 units/ml a dose of 1–80 units per injection, in steps of 1 unit, can be administered.
With Tresiba® 200 units/ml a dose of 2–160 units per injection, in steps of 2 units, can be administered. The dose is provided in half the volume of 100 units/ml basal insulin products.

The dose counter shows the number of units regardless of strength, and **no** dose conversion should be done when transferring a patient to a new strength.

Flexibility in dosing time
On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration (see *Pharmacodynamic properties*). A minimum of 8 hours between injections should always be ensured. There is no clinical experience with flexibility in dosing time of Tresiba® in children and adolescents.

Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule.

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

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

Transfer from other insulin medicinal products
Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

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

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

Patients with type 1 diabetes mellitus
For patients with type 1 diabetes, a dose reduction of 20% based on the previous basal insulin dose or basal component of a continuous subcutaneous insulin infusion regimen should be considered with subsequent individual dosage adjustments based on the glycaemic response.

Use of Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus
When adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

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

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

Renal and hepatic impairment: Tresiba® can be used in renal and hepatic impaired patients. Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see *Pharmacokinetic properties*).

Paediatric population: Tresiba® can be used in adolescents and children from the age of 1 year (see *Pharmacodynamic properties*). 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 *Special warnings and precautions for use*).

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® must not be drawn from the cartridge of the pre-filled pen into a syringe (see *Special warnings and precautions for use*).

Tresiba® is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see *Special warnings and precautions for use* and *Undesirable effects*).

Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying this leaflet (see *Special precautions for disposal and other handling*).

Tresiba® comes in a pre-filled pen (FlexTouch®) designed to be used with NovoFine® or NovoTwist® injection needles.
The 100 units/ml pre-filled pen delivers 1–80 units in steps of 1 unit.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients.*

Special warnings and precautions for use
Hypoglycaemia
Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.
In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.
Patients whose blood glucose control is greatly improved (e.g. by intensified insulin therapy) may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes.
Concomitant illness, especially infections and fever, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.
As with other basal insulin products, the prolonged effect of Tresiba® may delay recovery from hypoglycaemia.

Hyperglycaemia
Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia.
Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.
Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes mellitus, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

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

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

Combination of thiazolidinediones and insulin medicinal products
Cases of cardiac failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of thiazolidinediones and Tresiba® is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac symptoms occurs.

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

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

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

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying this leaflet (see *Special precautions for disposal and other handling*).

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Interaction with other medicinal products and other forms of interaction
A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the insulin requirement
Oral antidiabetic medicinal products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the insulin requirement
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

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

Fertility, pregnancy and lactation
Pregnancy
The use of Tresiba® in pregnant women with diabetes has been investigated in an interventional trial (see *Pharmacodynamic properties*). A moderate amount of clinical trial and post-marketing data in pregnant women (more than 400 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.
The treatment with Tresiba® may be considered during pregnancy, if clinically needed.
In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements usually return rapidly to pre-pregnancy values. Careful monitoring of glucose control is recommended and the insulin dose adjusted on an individual basis.

Breast-feeding
There is no clinical experience with Tresiba® during breast-feeding. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma.
It is unknown whether insulin degludec is excreted in human milk. No metabolic effects are anticipated in the breast-fed newborn/infant.

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

Effects on ability to drive and use machines
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).
Patients must be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Undesirable effects
Summary of the safety profile
The most frequently reported adverse reaction during treatment is hypoglycaemia (see *Description of selected adverse reactions* below).

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

System organ class	Frequency
Immune system disorders	*Rare* – Hypersensitivity
	Rare – Urticaria
Metabolism and nutrition disorders	*Very common* – Hypoglycaemia
Skin and subcutaneous tissue disorders	*Uncommon* – Lipodystrophy
	Not known – Cutaneous amyloidosis†
General disorders and administration site conditions	*Common* – Injection site reactions
	Uncommon – Peripheral oedema

† ADR from postmarketing sources.

Description of selected adverse reactions
Immune system disorders
With insulin preparations, allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening. With Tresiba®, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

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

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see *Special warnings and precautions for use*).

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

Paediatric population
Tresiba® has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see *Pharmacokinetic properties*). Safety and efficacy have 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 *Pharmacodynamic Properties*).

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

Overdose
A specific overdose for insulin cannot be defined. However, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required:
- Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries glucose-containing products.
- Severe hypoglycaemic episodes, where the patient is not able to treat himself, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: 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 ($AUC_{GIR,0-12h,SS}/AUC_{GIR,total,SS} = 0.5$).

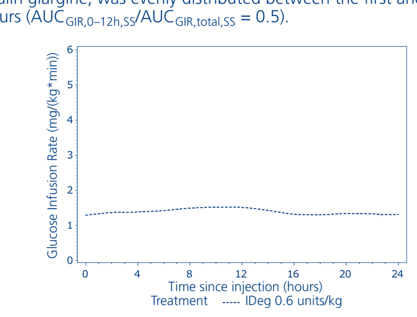


Figure 1 Glucose infusion rate profile, smoothed, steady state – Mean profile 0–24 hours – IDeg 100 units/ml 0.6 units/kg – Trial 1987

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

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

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

Clinical efficacy and safety
11 multinational clinical trials of 26 or 52 weeks' duration were conducted as controlled, open-label, randomised, parallel, treat-to-target trials exposing 4,275 patients to Tresiba® (1,102 in type 1 diabetes mellitus and 3,173 in type 2 diabetes mellitus).
In the open-label trials the effect of Tresiba® was tested in patients with type 1 diabetes mellitus (Table 2), in insulin naïve patients (insulin initiation in type 2 diabetes mellitus, Table 3) and in previous insulin users (insulin intensification in type 2 diabetes mellitus, Table 4) with fixed as well as flexible dosing time (Table 5), and the reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior in all trials against all comparators (insulin detemir and insulin glargine (100 units/ml)). While improvements in HbA_{1c} were non-inferior compared to other insulin products, against sitagliptin Tresiba® was statistically significantly superior in reducing HbA_{1c} (Table 4).
In a prospectively planned meta-analysis across seven open-label treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, Tresiba® was superior in terms of a lower number of treatment-emergent confirmed hypoglycaemic episodes (driven by a benefit in type 2 diabetes mellitus, see Table 1) and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine (100 units/ml) (administered according to label). The reduction in hypoglycaemia was achieved at a lower average FPG level with Tresiba® than with insulin glargine.

Table 1 Hypoglycaemia meta-analysis outcomes

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

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

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

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

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	Insulin glargine (100 units/ml)[1]	Tresiba®[1]	Insulin detemir[1]
N	**472**	**157**	**302**	**153**
HbA_{1c} (%)				
End of trial	7.3	7.3	7.3	7.3
Mean change	-0.40	-0.39	-0.73	-0.65
	Difference: -0.01 [-0.14; 0.11]		*Difference: -0.09 [-0.23; 0.05]*	
FPG (mmol/l)				
End of trial	7.8	8.3	7.3	8.9
Mean change	-1.27	-1.39	-2.60	-0.62
	Difference: -0.33 [-1.03; 0.36]		*Difference: -1.66 [-2.37; -0.95]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe	0.21	0.16	0.31	0.39
Confirmed[2]	42.54	40.18	45.83	45.69
	Ratio: 1.07 [0.89; 1.28]		*Ratio: 0.98 [0.80; 1.20]*	
Nocturnal confirmed[2]	4.41	5.86	4.14	5.93
	Ratio: 0.75 [0.59; 0.96]		*Ratio: 0.66 [0.49; 0.88]*	

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

Table 3 Results from open-label clinical trials in insulin naïve type 2 diabetes mellitus (insulin initiation)

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	Insulin glargine (100 units/ml)[1]	Tresiba®[1]	Insulin glargine (100 units/ml)[1]
N	**773**	**257**	**228**	**229**
HbA_{1c} (%)				
End of trial	7.1	7.0	7.0	6.9
Mean change	-1.06	-1.19	-1.30	-1.32
	Difference: 0.09 [-0.04; 0.22]		*Difference: 0.04 [-0.11; 0.19]*	
FPG (mmol/l)				
End of trial	5.9	6.4	5.9	6.3
Mean change	-3.76	-3.30	-3.70	-3.38
	Difference: -0.43 [-0.74; -0.13]		*Difference: -0.42 [-0.78; -0.06]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe	0	0.02	0	0
Confirmed[2]	1.52	1.85	1.22	1.42
	Ratio: 0.82 [0.64; 1.04]		*Ratio: 0.86 [0.58; 1.28]*	
Nocturnal confirmed[2]	0.25	0.39	0.18	0.28
	Ratio: 0.64 [0.42; 0.98]		*Ratio: 0.64 [0.30; 1.37]*	

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

Table 4 Results from open-label clinical trials in type 2 diabetes mellitus: left – prior basal insulin users, right – insulin naïve

	52 weeks of treatment		26 weeks of treatment	
	Tresiba®[1]	Insulin glargine (100 units/ml)[1]	Tresiba®[2]	Sitagliptin[2]
N	**744**	**248**	**225**	**222**
HbA_{1c} (%)				
End of trial	7.1	7.1	7.2	7.7
Mean change	-1.17	-1.29	-1.56	-1.22
	Difference: 0.08 [-0.05; 0.21]		*Difference: -0.43 [-0.61; -0.24]*	
FPG (mmol/l)				
End of trial	6.8	7.1	6.2	8.5
Mean change	-2.44	-2.14	-3.22	-1.39
	Difference: -0.29 [-0.65; 0.06]		*Difference: -2.17 [-2.59; -1.74]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe hypoglycaemia	0.06	0.05	0.01	0
Confirmed[3]	11.09	13.63	3.07	1.26
	Ratio: 0.82 [0.69; 0.99]		*Ratio: 3.81 [2.40; 6.05]*	
Nocturnal confirmed[3]	1.39	1.84	0.52	0.30
	Ratio: 0.75 [0.58; 0.99]		*Ratio: 1.93 [0.90; 4.10]*	

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

Table 5 Results from an open-label clinical trial with flexible dosing of Tresiba® in type 2 diabetes mellitus

	26 weeks of treatment		
	Tresiba®[1]	Tresiba® Flex[2]	Insulin glargine (100 units/ml)[3]
N	**228**	**229**	**230**
HbA_{1c} (%)			
End of trial	7.3	7.2	7.1
Mean change	-1.07	-1.28	-1.26
	Difference: -0.13 [-0.29; 0.03][5]		*Difference: 0.04 [-0.12; 0.20]*
FPG (mmol/l)			
End of trial	5.8	5.8	6.2
Mean change from baseline	-2.91	-3.15	-2.78
	Difference: -0.05 [-0.45; 0.35][5]		*Difference: -0.42 [-0.82; -0.02]*
Rate of hypoglycaemia (per patient year of exposure)			
Severe	0.02	0.02	0.02
Confirmed[4]	3.63	3.64	3.48
	Ratio: 1.10 [0.79; 1.52][6]		*Ratio: 1.03 [0.75; 1.40]*
Nocturnal confirmed[4]	0.56	0.63	0.75
	Ratio: 1.18 [0.66; 2.12][6]		*Ratio: 0.77 [0.44; 1.35]*

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

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

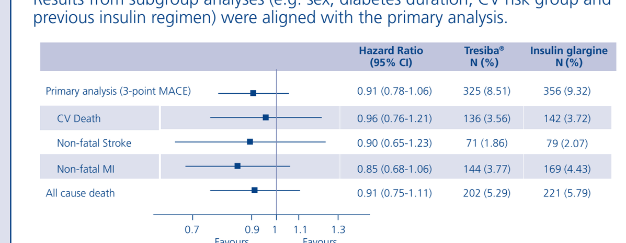
Furthermore, two 64-week controlled, double-blind, randomised, cross-over, treat-to-target trials were conducted in patients with at least one risk factor for hypoglycaemia and with type 1 diabetes mellitus (501 patients) or type 2 diabetes mellitus (721 patients). Patients were randomised to either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

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

	Type 1 diabetes mellitus		Type 2 diabetes mellitus	
	Tresiba®[1]	Insulin glargine (100 units/ml)[1]	Tresiba®[2]	Insulin glargine (100 units/ml)[2]
N	**501**		**721**	
HbA_{1c} (%)				
Baseline	7.6		7.6	
End of treatment	6.9	6.9	7.1	7.0
FPG (mmol/l)				
Baseline	9.4		7.6	
End of treatment	7.5	8.4	6.0	6.1
Rate of severe hypoglycaemia[3]				
Maintenance period[4]	0.69	0.92	0.05	0.09
	Ratio: 0.65 [0.48; 0.89]		*Ratio: 0.54 [0.21; 1.42]*	
Rate of severe or BG confirmed symptomatic hypoglycaemia[3,5]				
Maintenance period[4]	22.01	24.63	1.86	2.65
	Ratio: 0.89 [0.85; 0.94]		*Ratio: 0.70 [0.61; 0.80]*	
Rate of severe or BG confirmed symptomatic nocturnal hypoglycaemia[3,5]				
Maintenance period[4]	2.77	4.29	0.55	0.94
	Ratio: 0.64 [0.56; 0.73]		*Ratio: 0.58 [0.46; 0.74]*	

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

Cardiovascular evaluation
DEVOTE was a randomised, double-blind, and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of Tresiba® versus insulin glargine (100 units/ml) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events.
The primary analysis was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was designed as a non-inferiority trial to exclude a pre-specified risk margin of 1.3 for the hazard ratio (HR) of MACE comparing Tresiba® to insulin glargine. The cardiovascular safety of Tresiba® as compared to insulin glargine was confirmed (HR 0.91 [0.78; 1.06]) (Figure 2).
Results from subgroup analyses (e.g. sex, diabetes duration, CV risk group and previous insulin regimen) were aligned with the primary analysis.



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

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

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

Table 7 Results from DEVOTE

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

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

Pregnancy
Tresiba® has been studied in an open-label, randomised, active controlled clinical trial, in which pregnant women with type 1 diabetes mellitus were treated within a basal-bolus treatment regimen with Tresiba® (92 women) or insulin detemir (96 women) as basal insulin, both in combination with insulin aspart as meal time insulin (EXPECT).
Tresiba® was non-inferior to insulin detemir as measured by HbA_{1c} at last planned HbA_{1c} visit prior to delivery after gestational week (GW) 16. Moreover, no difference between treatment groups was observed for glycaemic control (change in HbA_{1c}, FPG and postprandial glucose (PPG)) during pregnancy.
No clinically relevant differences were observed between Tresiba® and insulin detemir for the maternal safety endpoints: hypoglycaemia, pre-term delivery and adverse events during the pregnancy. Pre-eclampsia was reported in 12 subjects treated with Tresiba® (13.2%) and in 7 subjects (7.4%) who were treated with insulin detemir. Non-planned caesarean section was reported in 23 subjects (25.3%) treated with Tresiba® and in 15 subjects (16.0%) treated with insulin detemir. The majority of the adverse events reported in both groups were non-serious, mild in severity, unlikely related to the trial product and had the outcome 'recovered/resolved'. No deaths were reported in the subjects who were randomised in the trial.

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

Paediatric population
The efficacy and safety of Tresiba® have been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). Patients in the Tresiba® arm included 43 children aged 1–5 years, 70 children aged 6–11 years and 61 adolescents aged 12–17 years. Tresiba® dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba® compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 versus 0.33), confirmed hypoglycaemia (57.71 versus 54.05) and nocturnal confirmed hypoglycaemia (6.03 versus 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. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population. 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.

Pharmacokinetic properties
Absorption
After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation.
Steady-state serum concentration is reached after 2–3 days of daily Tresiba® administration.
During a period of 24 hours with once-daily treatment, the exposure of insulin degludec was evenly distributed between the first and second 12 hours. The ratio between $AUC_{IDeg,0-12h,SS}$ and $AUC_{IDeg,\tau,SS}$ was 0.5.

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

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

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

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

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

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

Paediatric population
The 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.

Preclinical safety data
Non-clinical data reveal no safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction.
The ratio of mitogenic relative to metabolic potency for insulin degludec is comparable to that of human insulin.

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

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

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 it from light.

After first opening or carried as a spare:
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).
Keep the cap on the pen in order to protect it from light.

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

Special precautions for disposal and other handling
This medicinal product is for use by one person only. It must not be refilled.
Tresiba® must not be used if the solution does not appear clear and colourless.
Tresiba® which has been frozen must not be used.

A new needle must always be attached before each use. Needles must not be re-used. The patient should discard the needle after each injection.
In the event of blocked needles, patients must follow the instructions described in the instructions for use, see overleaf.

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

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

Tresiba® 100 units/ml packaging and label are light green.
The pre-filled pen (FlexTouch®) is designed to be used with NovoFine®/NovoTwist® injection needles up to a length of 8 mm.
It delivers 1–80 units in steps of 1 unit.

For detailed instructions for use, see overleaf.

Marketing authorisation holder
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

novo nordisk®

8-9560-00-011-1

TRESIBA®
FlexTouch® 100 units/ml

novo nordisk®

8 mm
1 mm

Length: Max. 20 mm (100%)
Code: 100% Direction →
Code centered

8-9560-00-011-1.indd 1

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

Please read these instructions carefully before using your FlexTouch® pre-filled pen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

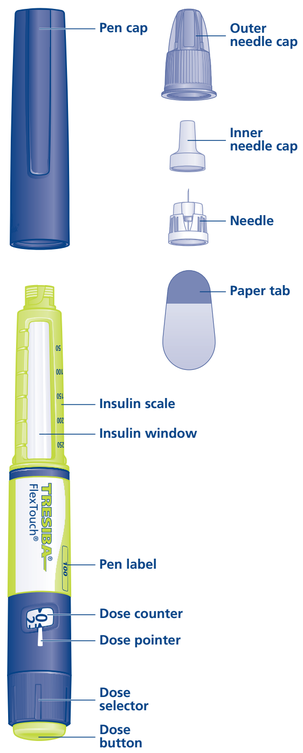
Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains Tresiba® 100 units/ml,** then look at the illustrations below to get to know the different parts of your pen and needle.

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

Your pen is a pre-filled dial-a-dose insulin pen containing 300 units of insulin. You can select a **maximum of 80 units per dose, in steps of 1 unit.** Your pen is designed to be used with NovoTwist® or NovoFine® single-use disposable needles up to a length of 8 mm. Needles are not included in the pack.

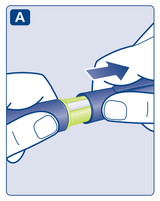
⚠ **Important information**
Pay special attention to these notes as they are important for correct use of the pen.

Tresiba® FlexTouch® pen and needle (example)

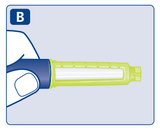


1. Prepare your pen

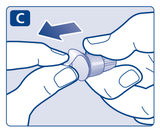
- **Check the name and strength on the label** of your pen, to make sure that it contains Tresiba® 100 units/ml. This is especially important if you take more than one type of insulin. If you take a wrong type of insulin, your blood sugar level may get too high or too low.
- **Pull off the pen cap.**



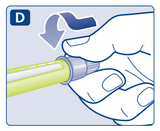
- **Check that the insulin in your pen is clear** and colourless. Look through the insulin window. If the insulin looks cloudy, do not use the pen.



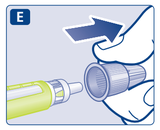
- **Take a new needle** and tear off the paper tab.



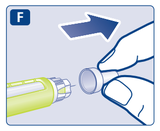
- **Push the needle straight onto the pen. Turn until it is on tight.**



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



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

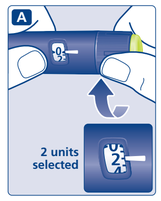


⚠ **Always use a new needle for each injection.**
This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

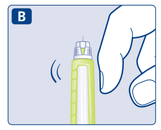
⚠ **Never use a bent or damaged needle.**

2. Check the insulin flow

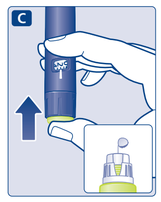
- **Always check the insulin flow before you start. This helps you to ensure that you get your full insulin dose.**
- Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**



- Hold the pen with the needle pointing up.
  Tap the top of the pen gently a few times to let any air bubbles rise to the top.



- **Press and hold in the dose button** until the dose counter returns to 0. The 0 must line up with the dose pointer.
  A drop of insulin should appear at the needle tip.



A small air bubble may remain at the needle tip, but it will not be injected.

If no drop appears, repeat steps 2**A** to 2**C** up to 6 times. If there is still no drop, change the needle and repeat steps 2**A** to 2**C** once more.

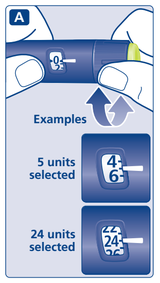
If a drop of insulin still does not appear, dispose of the pen and use a new one.

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

⚠ **Always check the flow before you inject.** If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

3. Select your dose

- **Make sure the dose counter shows 0 before you start.** The 0 must line up with the dose pointer.
- **Turn the dose selector to select the dose you need,** as directed by your doctor or nurse.
  If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  The pen can dial up to a maximum of 80 units.



The dose selector changes the number of units. Only the dose counter and dose pointer will show how many units you select per dose.

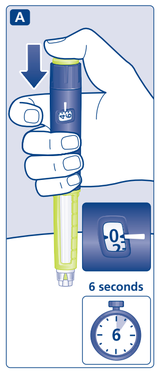
You can select up to 80 units per dose. When your pen contains less than 80 units, the dose counter stops at the number of units left.

The dose selector clicks differently when turned forwards, backwards or past the number of units left. Do not count the pen clicks.

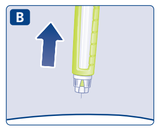
⚠ **Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.**
Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the insulin scale, it only shows approximately how much insulin is left in your pen.

4. Inject your dose

- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.**
  Do not touch the dose counter with your fingers. This could interrupt the injection.
- **Press and hold down the dose button until the dose counter returns to 0.**
  The 0 must line up with the dose pointer.
  You may then hear or feel a click.
- **Leave the needle under the skin for at least 6 seconds** to make sure you get your full dose.



- **Pull the needle and pen straight up from your skin.** If blood appears at the injection site, press lightly with a cotton swab. Do not rub the area.

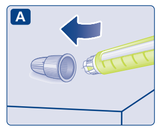


You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your dose.

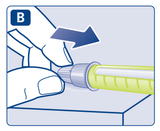
⚠ **Always watch the dose counter to know how many units you inject.**
The dose counter will show the exact number of units.
Do not count the pen clicks.
Hold the dose button down until the dose counter returns to 0 after the injection. If the dose counter stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.

5. After your injection

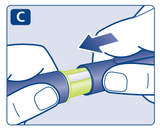
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer cap.



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



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



Always dispose of the needle after each injection.
This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. If the needle is blocked, you will **not** inject any insulin.

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

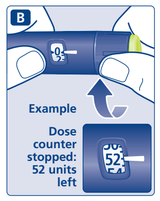
⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

⚠ **Always remove the needle after each injection** and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

6 How much insulin is left?

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

- **To see precisely how much insulin is left,** use the dose counter:
  Turn the dose selector until the **dose counter stops.** If it shows 80, **at least 80** units are left in your pen.
  If it shows **less than 80,** the number shown is the number of units left in your pen.
- Turn the dose selector back until the dose counter shows 0.
- If you need more insulin than the units left in your pen, you can split your dose between two pens.



⚠ **Be very careful to calculate correctly if splitting your dose.**
If in doubt, take the full dose with a new pen. If you split the dose wrong, you will inject too little or too much insulin, which can lead to too high or too low blood sugar level.

⚠ Further important information

- **Always keep your pen with you.**
- **Always carry an extra pen and new needles** with you, in case of loss or damage.
- Always keep your pen and needles **out of sight and reach of others,** especially children.
- **Never share** your pen or your needles with other people. It might lead to cross-infection.
- **Never share** your pen with other people. Your medicine might be harmful to their health.
- Caregivers must **be very careful when handling used needles** – to reduce the risk of needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

- **Do not leave the pen in a car** or other place where it can get too hot or too cold.
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth.
- **Do not drop your pen** or knock it against hard surfaces.
  If you drop it or suspect a problem, attach a new needle and check the insulin flow before you inject.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.