

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

▼ 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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 100 units insulin glargine* (equivalent to 3.64 mg).

Each pen contains 3 mL of solution for injection, equivalent to 300 units.

*Insulin glargine is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection). Nexvue.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

LUSDUNA contains insulin glargine, an insulin analogue, and has a prolonged duration of action. LUSDUNA should be administered once daily at any time but at the same time each day.

The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, LUSDUNA can also be given together with oral antidiabetic medicinal products.

The potency of this medicinal product is stated in units. These units are exclusive to insulin glargine and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Special populations

Elderly population (≥ 65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Paediatric population

Safety and efficacy of insulin glargine have been established in adolescents and children aged 2 years and older. Currently available data are described in sections 4.8, 5.1 and 5.2.

Safety and efficacy of insulin glargine have not been established in children below the age of 2 years. No data are available.

Switch from other insulins to LUSDUNA

When changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with LUSDUNA, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products).

Switch from twice daily NPH insulin to LUSDUNA

To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with LUSDUNA should reduce their daily dose of basal insulin by 20-30 % during the first weeks of treatment.

Switch from insulin glargine 300 units/mL to LUSDUNA

LUSDUNA and medicinal products containing insulin glargine 300 units/mL are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycaemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily insulin glargine 300 units/mL to a once daily regimen with LUSDUNA should reduce their dose by approximately 20%.

During the first weeks the reduction should, at least partially, be compensated by an increase in mealtime insulin, after this period the regimen should be adjusted individually.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dose regimen may become necessary. Dose adjustment may also be required, for example, if the patient's weight or life-style changes, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (see section 4.4).

Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with LUSDUNA.

Method of administration

LUSDUNA is only suitable for subcutaneous injections via a disposable pen. If administration by syringe is necessary, another insulin glargine product available in a vial should be used.

LUSDUNA should not be administered intravenously. The prolonged duration of action of insulin glargine is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of insulin glargine. Injection sites must be rotated within a given injection area from one injection to the next to prevent injection site reactions (see section 4.8).

LUSDUNA must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Before using Nexvue, the instructions for use included in the pack must be read carefully (see section 6.6).

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

LUSDUNA is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

Hypoglycaemia

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Due to more sustained basal insulin supply with insulin glargine, less nocturnal but more early morning hypoglycaemia can be expected.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- who have experienced recurrent and/or recent events of hypoglycaemia,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insulin antibodies formation

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 (see section 5.1).

Medication errors

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins.

Combination of LUSDUNA with pioglitazone

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 heart failure. This should be kept in mind if treatment with the combination of pioglitazone and LUSDUNA 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.

Excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e., essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of insulin glargine.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates, somatostatin analogues and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors.

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor foeto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity.

The use of LUSDUNA may be considered during pregnancy, if clinically needed.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycaemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding

It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breastfed newborn/infant are anticipated since insulin glargine as a peptide is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate direct harmful effects with respect to 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 or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia (very common), in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement (see section 4.4).

Tabulated list of adverse reactions

The following related adverse reactions from clinical trials are listed below as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: $\geq 1/10$; common: $\geq 1/100$ to $< 1/100$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ to $< 1/1,000$; very rare: $< 1/10,000$).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders					
				Allergic reactions	
Metabolism and nutrition disorders					
	Hypoglycaemia				
Nervous system disorders					
					Dysgeusia
Eye disorders					
				Visual impairment Retinopathy	
Skin and subcutaneous tissue disorders					
		Lipohypertrophy	Lipoatrophy		
Musculoskeletal and connective tissue disorders					
					Myalgia
General disorders and administration site conditions					
		Injection site reactions		Oedema	

Description of selected adverse reactions

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms (see section 4.4).

Immune system disorders

Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock, and may be life-threatening.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

Lipodystrophy 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.

General disorders and administration site conditions

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Rarely, insulin may cause sodium retention and oedema particularly if previously poor metabolic control is improved by intensified insulin therapy.

Paediatric population

In general, the safety profile for children and adolescents (≤ 18 years of age) is similar to the safety profile for adults.

The adverse reaction reports received from post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤ 18 years of age) than in adults.

Clinical study safety data are not available for children under 2 years.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting.
ATC Code: A10AE04.

LUSDUNA is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Mechanism of action

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the LUSDUNA injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 5.2).

Insulin receptor binding: *In vitro* studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin.

The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in LUSDUNA therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

Pharmacodynamic effects

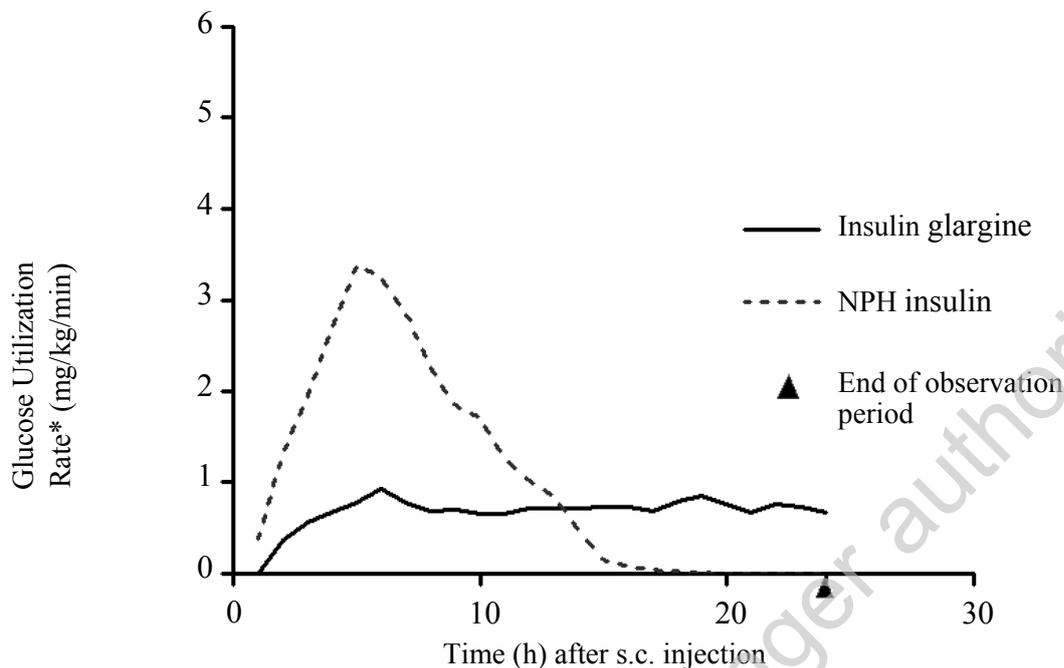
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables.

In euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged.

The following graph shows the results from a study in patients:

Figure 1: Activity Profile in Patients with Type 1 Diabetes



*determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values)

The longer duration of action of subcutaneous insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.

In a clinical study, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes.

In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed with the same frequency in both NPH-insulin and insulin glargine treatment groups.

Clinical efficacy and safety

Effects of insulin glargine (once daily) on diabetic retinopathy were evaluated in an open-label 5 year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when insulin glargine was compared to NPH insulin.

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicentre, randomised, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12 % of participants) or type 2 diabetes mellitus treated with ≤ 1 antidiabetic oral agent (88 % of participants). Participants were randomized (1:1) to receive insulin glargine (n=6,264), titrated to reach FPG ≤ 95 mg/dL (5.3 mM), or standard care (n=6,273).

The first co-primary efficacy outcome was the time to the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, and the second co-primary efficacy outcome was the

time to the first occurrence of any of the first co-primary events, or revascularisation procedure (coronary, carotid, or peripheral), or hospitalisation for heart failure.

Secondary endpoints included all-cause mortality and a composite microvascular outcome.

Insulin glargine did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co-primary outcomes; for any component endpoint comprising these outcomes; for all-cause mortality; or for the composite microvascular outcome.

Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4 % and median on-treatment HbA1c values ranged from 5.9 to 6.4 % in the insulin glargine group, and 6.2 % to 6.6 % in the standard care group throughout the duration of follow-up. The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6-year study, 42 % of the insulin glargine group did not experience any hypoglycaemia.

At the last on-treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.

Paediatric population

In a randomised, controlled clinical study, paediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohaemoglobin and the incidence of symptomatic hypoglycaemia were observed in both treatment groups, however fasting plasma glucose decreased more from baseline in the insulin glargine group than in the NPH group. There was less severe hypoglycaemia in the insulin glargine group as well. One hundred forty three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension study with mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.

A crossover study comparing insulin glargine plus lispro insulin to NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed. As in the paediatric study described above, fasting plasma glucose reduction from baseline was greater in the insulin glargine group than in the NPH group. HbA1c changes from baseline were similar between treatment groups; however blood glucose values recorded overnight were significantly higher in the insulin glargine/ lispro group than the NPH/regular group, with a mean nadir of 5.4 mM versus 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycaemia were 32 % in the insulin glargine / lispro group versus 52 % in the NPH / regular group.

A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 2 to 6 years, comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin. Both groups received bolus insulin before meals.

The primary aim of demonstrating non-inferiority of insulin glargine to NPH in all hypoglycaemia was not met and there was a trend to an increase of hypoglycaemic events with insulin glargine [insulin glargine: NPH rate ratio (95 % CI) = 1.18 (0.97-1.44)]. Glycohaemoglobin and glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this study.

5.2 Pharmacokinetic properties

Absorption

In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin. Concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine. Figure 1 above shows the activity profiles over time of insulin glargine and NPH insulin.

Insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose.

Biotransformation

After subcutaneous injection in diabetic patients, insulin glargine is rapidly metabolised at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of insulin glargine.

The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine is principally based on exposure to M1. Insulin glargine and the metabolite M2 were not detectable in the vast majority of subjects and, when they were detectable their concentration was independent of the administered dose of insulin glargine.

Elimination

When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.

Special populations

In clinical studies, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy in insulin glargine-treated patients compared to the entire study population.

Paediatric population

Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study (see section 5.1). Plasma “trough” levels of insulin glargine and its main M1 and M2 metabolites were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

Shelf-life after removing the pen from the refrigerator

The medicinal product may be stored for a maximum of 28 days up to 30°C and away from direct heat or direct light. Pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Before use

Store in a refrigerator (2°C – 8°C).

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In use

For storage conditions after removing this medicinal product from the refrigerator, see section 6.3.

6.5 Nature and contents of container

Cartridge (type I colourless glass) with a plunger (bromobutyl rubber) and aluminium combi-seal fitted with a bi-layered bromobutyl rubber and polyisoprene rubber flat disc containing 3 mL of solution.

The cartridge is sealed in a disposable pen injector.

Packs of 1, 5 and multipacks containing 10 (2 packs of 5) pens. Not all pack sizes may be marketed.

Needles are not included in the pack.

6.6 Special precautions for disposal and other handling

Before first use, the pen must be stored at room temperature for 1 to 2 hours to allow it to warm up. Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since LUSDUNA is a solution, it does not require resuspension before use.

LUSDUNA must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Empty pens must never be reused and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins (see section 4.4).

Before using Nexvue, the instructions for use included in the pack must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1162/001
EU/1/16/1162/002
EU/1/16/1162/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Merck Sharp & Dohme Corp. Elkton, VA
Stonewall Plant
2778 South East Side Highway
Elkton, Virginia 22827
UNITED STATES

Name and address of the manufacturer(s) responsible for batch release

N.V. Organon
Molenstraat 110
5342 CC Oss
NETHERLANDS

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

• **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - Packs of 1 and 5

1. NAME OF THE MEDICINAL PRODUCT

LUSDUNA 100 units/mL solution for injection in a pre-filled pen
Insulin glargine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 100 units (3.64 mg) insulin glargine.

3. LIST OF EXCIPIENTS

Excipients: zinc chloride, metacresol, glycerol, hydrochloric acid and sodium hydroxide (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, Nexvue.
1 pre-filled pen of 3 mL
5 pre-filled pens of 3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Carefully read the instructions for use included in the pack before using Nexvue.
QR code linking to the instructions for use to be included. Instructions for use online at www.lusdunanexvue.com

Read the package leaflet before use.

Subcutaneous use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard pen 28 days after removal from refrigerator.

9. SPECIAL STORAGE CONDITIONSBefore use

Store in a refrigerator.

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In use

Store below 30°C.

Do not refrigerate or freeze.

Recap the pen after use in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.

Waarderweg 39

2031 BN Haarlem

The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1162/001 1 pre-filled pen of 3 mL

EU/1/16/1162/002 5 pre-filled pens of 3 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

LUSDUNA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (without blue box) component of a multipack – 5 pens

1. NAME OF THE MEDICINAL PRODUCT

LUSDUNA 100 units/mL solution for injection in a pre-filled pen
Insulin glargine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 100 units (3.64 mg) insulin glargine.

3. LIST OF EXCIPIENTS

Excipients: zinc chloride, metacresol, glycerol, hydrochloric acid and sodium hydroxide (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, Nexvue.

5 pre-filled pens of 3 mL. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTES OF ADMINISTRATION

Carefully read the instructions for use included in the pack before using Nexvue.
QR code linking to the instructions for use to be included. Instructions for use online at www.lusdunanexvue.com

Read the package leaflet before use.

Subcutaneous use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard pen 28 days after removal from refrigerator.

9. SPECIAL STORAGE CONDITIONSBefore use

Store in a refrigerator.

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In use

Store below 30°C.

Do not refrigerate or freeze.

Recap the pen after use in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1162/003 5 pre-filled pens of 3 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

LUSDUNA

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with blue box) multipack – 10 (2 x 5)

1. NAME OF THE MEDICINAL PRODUCT

LUSDUNA 100 units/mL solution for injection in a pre-filled pen
Insulin glargine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 100 units (3.64 mg) insulin glargine.

3. LIST OF EXCIPIENTS

Excipients: zinc chloride, metacresol, glycerol, hydrochloric acid and sodium hydroxide (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, Nexvue.

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

5. METHOD AND ROUTES OF ADMINISTRATION

Carefully read the instructions for use included in the package before using Nexvue.
QR code linking to the instructions for use to be included. Instructions for use online at www.lusdunanexvue.com

Read the package leaflet before use.

Subcutaneous use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard pen 28 days after removal from refrigerator.

9. SPECIAL STORAGE CONDITIONS

Before use

Store in a refrigerator.

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In use

Store below 30°C.

Do not refrigerate or freeze.

Recap the pen after use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1162/003 10 (2 packs of 5) pre-filled pens of 3 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUSDUNA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING

PEN LABEL –NEXVUE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LUSDUNA 100 units/mL injection
Nexvue
Insulin glargine
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Date out of the refrigerator: Write-in space for placing date the pen was out of refrigerator.

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Package leaflet: Information for the user

LUSDUNA 100 units/mL solution for injection in a pre-filled pen Insulin glargine

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

Read all of this leaflet carefully including the LUSDUNA Nexvue pre-filled pen Instructions for Use, before you start using this medicine because it contains important information for you.

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

What is in this leaflet

1. What LUSDUNA is and what it is used for
2. What you need to know before you use LUSDUNA
3. How to use LUSDUNA
4. Possible side effects
5. How to store LUSDUNA
6. Contents of the pack and other information

1. What LUSDUNA is and what it is used for

LUSDUNA contains insulin glargine. This is a modified insulin, very similar to human insulin.

LUSDUNA is used to treat diabetes mellitus in adults, adolescents and children aged 2 years and above.

Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insulin glargine has a long and steady blood-sugar-lowering action.

2. What you need to know before you use LUSDUNA

Do not use LUSDUNA

- If you are allergic to insulin glargine or any of the other ingredients of this medicine (listed in section 6).

LUSDUNA is only suitable for injection just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using LUSDUNA.

Follow closely the instructions for posology, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see section “Hyperglycaemia and Hypoglycaemia” at the end of this leaflet).

Travel

Before travelling consult your doctor. You may need to talk about:

- the availability of your insulin in the country you are visiting,
- supplies of insulin, syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require a lot of care (for example, adjustment to insulin dose, blood and urine tests):

- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

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

Children

There is no experience with the use of LUSDUNA in children below the age of 2 years.

Other medicines and LUSDUNA

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:

- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as acetylsalicylic acid, used to relieve pain and lower fever),
- somatostatin analogues (such as octreotide, used to treat an uncommon condition in which you make too much growth hormone),
- sulphonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:

- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat low blood sugar),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- atypical antipsychotic medicines (such as clozapine, olanzapine),
- protease inhibitors (used to treat HIV).

Your blood sugar level may either rise or fall if you take:

- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise hypoglycaemia. If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

LUSDUNA with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:

- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:

- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of LUSDUNA

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

3. How to use LUSDUNA

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

LUSDUNA is only suitable for injection just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Switching insulins

Although LUSDUNA contains the same active substance as other medicines containing insulin glargine 300 units/ml, these medicines are not interchangeable. The switch from one insulin therapy to another requires medical prescription, medical supervision and blood glucose monitoring. Please, consult your doctor for further information.

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will

- determine how much LUSDUNA per day you will need and at what time,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of LUSDUNA.

LUSDUNA is a long-acting insulin. Your doctor may tell you to use it in combination with a short-acting insulin or with tablets used to treat high blood sugar levels.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See section "Hyperglycaemia and Hypoglycaemia" at the end of this leaflet.

Use in children and adolescents

LUSDUNA can be used in adolescents and children aged 2 years and above. Use this medicine exactly as your doctor has told you.

Frequency of administration

You need one injection of LUSDUNA every day, at the same time of the day. The Nexvue pen delivers LUSDUNA in increments of 1 unit up to a maximum single dose of 60 units. The pen contains a total of 300 units.

Method of administration

LUSDUNA is injected under the skin. Do not inject LUSDUNA in a vein, since this will change its action and may cause hypoglycaemia.

Your doctor will show you in which area of the skin you should inject LUSDUNA. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle Nexvue

Nexvue is a pre-filled disposable pen containing insulin glargine.

Read carefully the "Nexvue Instructions for Use" included in this pack. You must use the pen as described in these Instructions for Use.

A new needle must be attached before each use. Only use needles that are compatible for use with Nexvue (see "Nexvue Instructions for Use").

A safety test must be performed before each injection.

Look at the cartridge before you use the pen. Do not use Nexvue if you notice particles in it. Only use Nexvue if the solution is clear, colourless and waterlike. Do not shake or mix it before use.

To prevent the possible transmission of disease, never share your pen with anyone else. This pen is only for your use.

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with Nexvue, consult your doctor, pharmacist or nurse.

Empty pens must not be re-filled and must be properly discarded.

Do not use Nexvue if it is damaged or not working properly; it has to be discarded and a new pen has to be used.

Insulin mix-ups

You must always check the insulin label before each injection to avoid mix-ups between LUSDUNA and other insulins.

If you use more LUSDUNA than you should

- If you **have injected too much LUSDUNA**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see section “Hyperglycaemia and Hypoglycaemia” at the end of this leaflet.

If you forget to use LUSDUNA

- If you **have missed a dose of LUSDUNA** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see section “Hyperglycaemia and Hypoglycaemia” at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using LUSDUNA

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop LUSDUNA without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

If you notice signs of your blood sugar being too low (hypoglycaemia), take action to increase your blood sugar level straight away (see section “Hyperglycaemia and Hypoglycaemia” at the end of this leaflet). Hypoglycaemia (low blood sugar) can be very serious and is very common with insulin treatment (may affect more than 1 in 10 people). Low blood sugar means that there is not enough sugar in your blood. If your blood sugar level falls too low, you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. For more information, see section “Hyperglycaemia and Hypoglycaemia” at the end of this leaflet.

Severe allergic reactions (rare, may affect up to 1 in 1,000 people) – the signs may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angioedema), shortness of breath, a fall in blood pressure with rapid heartbeat and sweating. Severe

allergic reactions to insulins may become life-threatening. Tell a doctor straight away if you notice signs of severe allergic reaction.

Common side effects (may affect up to 1 in 10 people)

- **Skin changes at the injection site**

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy, may affect up to 1 in 100 people) or thicken (lipohypertrophy). The insulin may not work very well. Change the injection site with each injection to help prevent these skin changes.

- **Skin and allergic reactions at the injection site**

These signs may include reddening, unusually intense pain when injecting, itching, hives, swelling or inflammation. This can spread around the injection site. Most minor reactions to insulins usually disappear in a few days to a few weeks.

Rare side effects (may affect up to 1 in 1,000 people)

- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

- **General disorders**

In rare cases, insulin treatment may also cause temporary build-up of water in the body, with swelling in the calves and ankles.

Very rare side-effects (may affect up to 1 in 10,000 people)

In very rare cases, dysgeusia (taste disorders) and myalgia (muscular pain) can occur.

Use in children and adolescents

In general, the side effects in children and adolescents of 18 years of age or less are similar to those seen in adults.

Complaints of injection site reactions (injection site reaction, injection site pain) and skin reactions (rash, urticaria) are reported relatively more frequently in children and adolescents of 18 years of age or less than in adults.

There is no experience in children under 2 years.

Reporting of side effects

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

5. How to store LUSDUNA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens

Store in a refrigerator (2°C – 8°C). Do not freeze.

Do not put LUSDUNA next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens

Pre-filled pens in use or carried as a spare may be stored for a maximum of 28 days up to 30°C and away from direct heat and direct light. The pen in use or carried as a spare must not be stored in the refrigerator. Do not use it after this time period.

Remove the needle after the injection and store the pen without the needle. The pen cap must be put back on the pen after each injection in order to protect from light.

Also, be sure to remove the needle before disposing of the pen. Needles must not be re-used.

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

6. Contents of the pack and other information

What LUSDUNA contains

- The active substance is insulin glargine. Each mL of the solution contains 100 units of the insulin glargine (equivalent to 3.64 mg). Each pen contains 3 mL of solution for injection (equivalent to 300 units).
- The other ingredients are: zinc chloride, metacresol, glycerol, sodium hydroxide (for pH adjustment) (see section 2 “Important information about some of the ingredients of LUSDUNA”), hydrochloric acid (for pH adjustment) and water for injections.

What LUSDUNA looks like and contents of the pack

LUSDUNA 100 units/mL solution for injection in a pre-filled pen is a clear and colourless solution.

Packs of 1, 5 and a multipack with 10 (2 x 5) pre-filled pens are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Manufacturer

NV Organon
Molenstraat 110
5342 CC Oss
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

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

Medicinal product no longer authorised

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

- Always carry some sugar (at least 20 grams) with you.
- Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and LUSDUNA").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heartbeat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:

- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and LUSDUNA").

Hypoglycaemia is also more likely to occur if

- you have just begun insulin treatment or changed to another insulin preparation (when changing from your previous basal insulin to LUSDUNA, hypoglycaemia, if it occurs, may be more likely to occur in the morning than at night),
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heartbeat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as LUSDUNA,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and LUSDUNA").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
The recovery of hypoglycaemia may be delayed because LUSDUNA has a long action.
3. If the hypoglycaemia comes back again, take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:

If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Medicinal product no longer authorised

Instructions for use

LUSDUNA 100 units/mL solution for injection in a pre-filled pen (Nexvue)

Insulin glargine



Needles and alcohol swabs are not included.

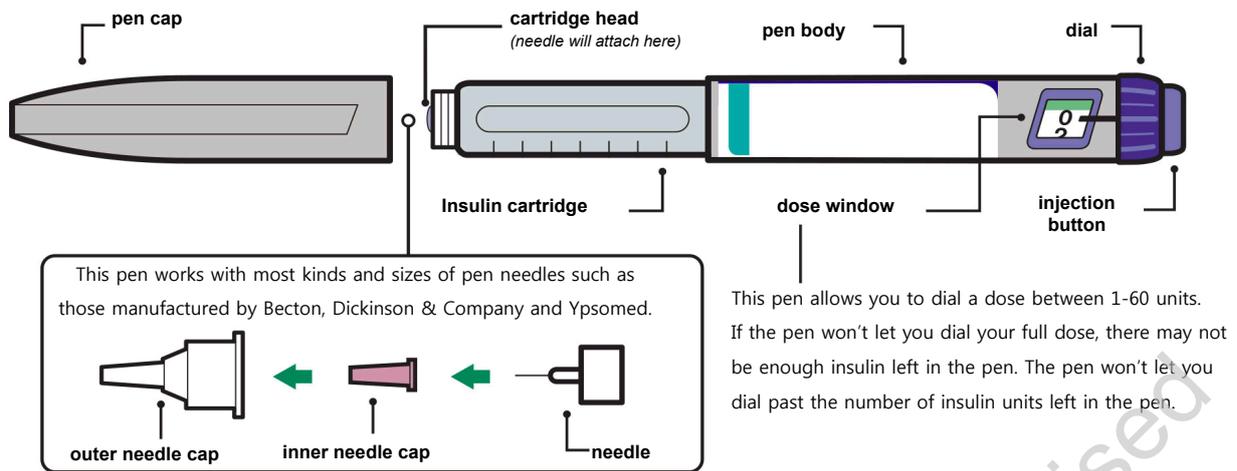
PLEASE READ THESE INSTRUCTIONS BEFORE USE.

Important information

- LUSDUNA contains a medicine called insulin glargine.
- If you use more than one type of medicine, make sure you have the right medicine before injecting.
- Your doctor or nurse will show you how to use your pen. If you haven't been trained before, ask your doctor or nurse to show you how to use your pen.
- Always attach a new needle before each use. Only use needles that are compatible for use with your pen (see section "Parts of your pen" below).
- Do not select a dose or press the injection button without a needle attached.
- Always perform the safety test before each injection.
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use the pen if it is damaged or if you are not sure that it is working properly.
- Always have a spare pen in case your pen is lost or damaged.

It is important that you know how your insulin helps you and how to avoid the most common side effect - low blood sugar (hypoglycaemia), which can be serious. Read about this in the Package leaflet supplied in every carton. If you have any questions about this medicine or diabetes, please ask your doctor or nurse for assistance.

Parts of your pen



Caring for your pen

New pens you haven't used before:

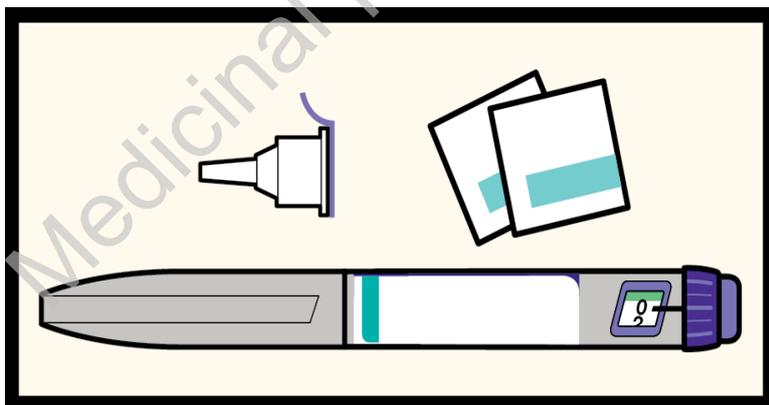
- Store pens in the box in the refrigerator (2°C- 8°C). Do not freeze. Make sure the pens are away from the freezer compartment or a freezer pack.
- If your pen is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Once you've opened and are using a pen:

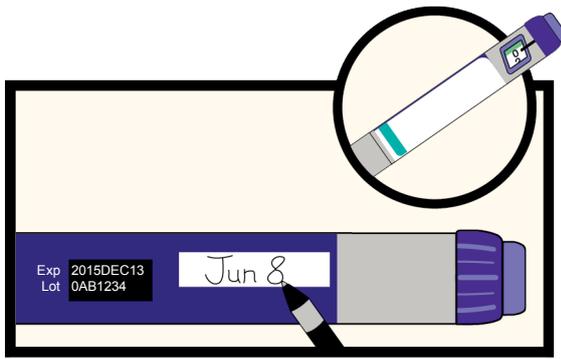
- Do not put it back in the refrigerator or freeze. You should keep it at room temperature (below 30°C).
- Keep it away from direct heat and light.
- You can clean the outside of your pen by wiping it with a damp cloth. Don't run your pen under water.
- Your pen is usable for up to 28 days after removal from the refrigerator.

1. Getting ready

Always check you have the right pen. If you use more than one type of medicine, make sure you have the right medicine before injecting.



Place a new sterile needle, two alcohol swabs and a pen on a clean, dry surface. Wash your hands before continuing.



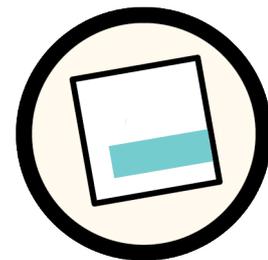
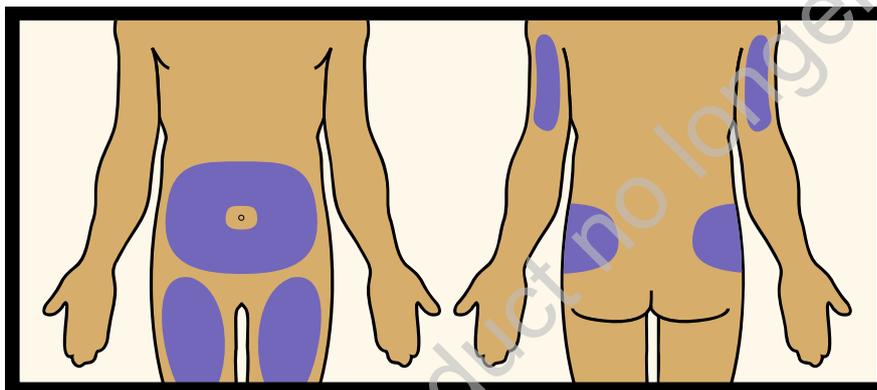
Always check both dates!

Write the date you removed your pen from the refrigerator on the label. Don't use your pen after the expiration date. Don't use your pen if it has been removed from the refrigerator for more than 28 days.

2. Prepare for your injection

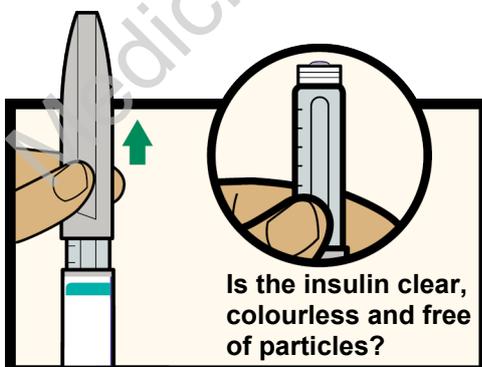
Choose your injection site

Your abdomen, thigh, or back of your upper arm, are the best sites for injection.



Clean your injection site

Clean the area with an alcohol swab. You should change injection site with each injection following the advice of your doctor.

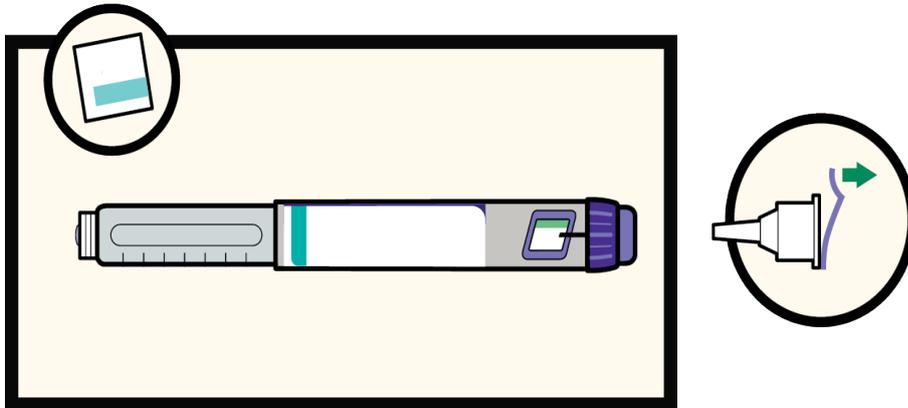


Check your insulin

Remove the pen cap. Check the cartridge to make sure the insulin is clear, colourless and free of particles. If not, get a new pen.

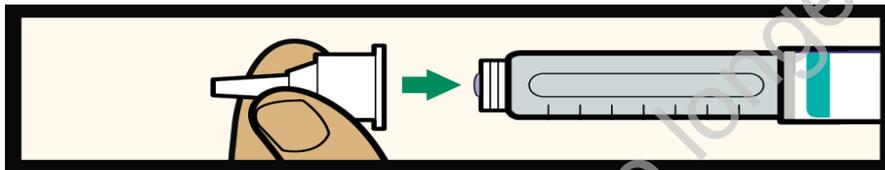
3. Attach a new needle

Clean the cartridge head with an alcohol swab. This kills germs that might make you sick.



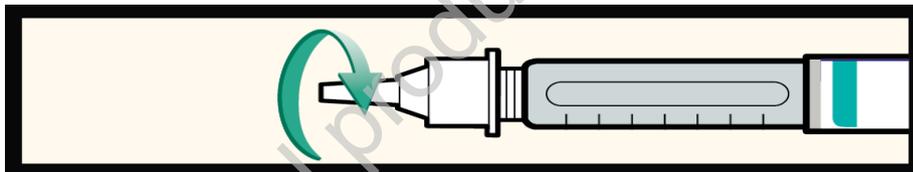
Open the needle

Remove the seal from the needle. Be careful you do not dirty the needle.



Push needle on

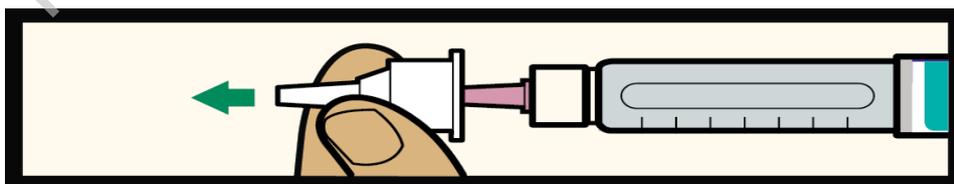
Push the needle onto the pen. Keep the needle straight so you do not damage the pen or needle.



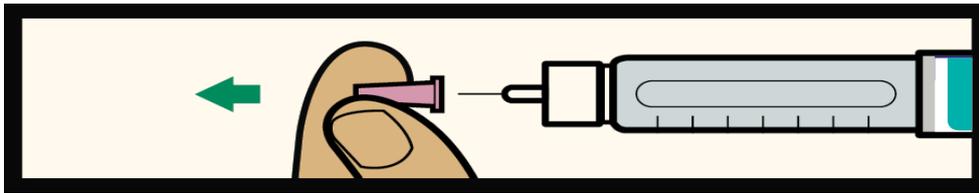
Screw needle

Screw the needle onto the pen to attach it.

4. Remove needle caps



Remove the outer needle cap and keep it. You'll need it again later.



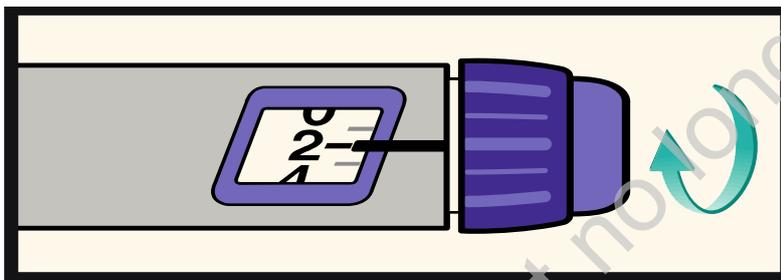
Remove inner needle cap and throw away

Inner needle cap must be removed before injecting the dose. Throw away the inner cap; you will not need it again.

Use a new needle each time. This helps to make sure you get the right insulin dose and it lowers your chances of any pain or illness from germs.

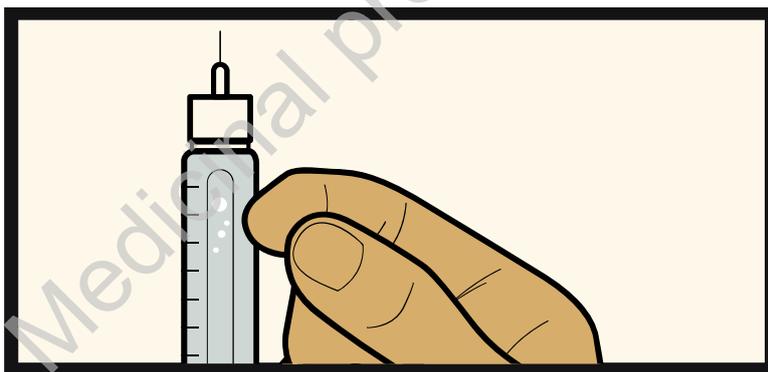
5. Do a safety check

Every time you inject you need to do a small test dose to make sure your pen is working. This step helps to ensure that you will get your full dose later on.



Dial a 2-unit test dose

Dial a test dose of two units by turning the dial until the black line points to “2”.

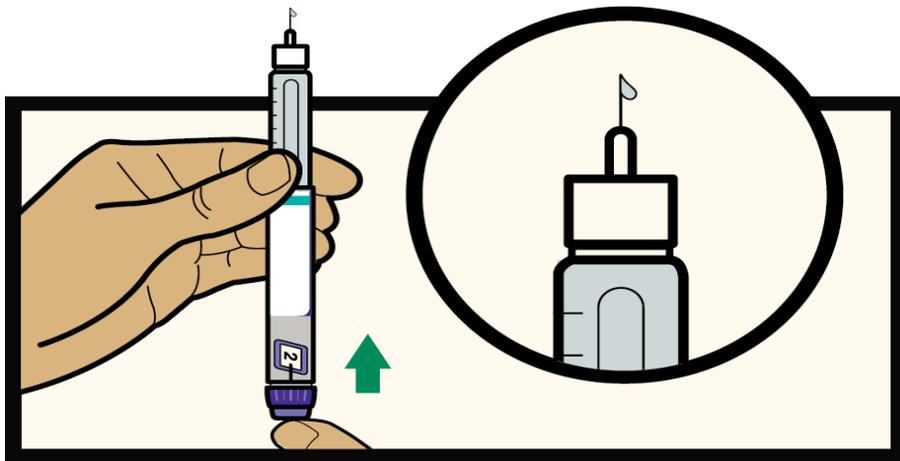


Tap the pen

Hold the pen upright and tap the cartridge gently to allow any air bubbles to rise to the top.

Press to inject into the air

Press the injection button all the way in while pointing the needle up into the air. Check to make sure insulin comes out of the pen.



Repeat until you see insulin

If no medicine comes out, dial 2 units again and press the injection button again. It may take up to five tries. If it does not work, you will need to try with a new needle. See Step 9 for how to remove a needle. If it does not work with a new needle, you will need to speak to your doctor or nurse.

Do a safety check each time you inject. This helps make sure you get your full dose of insulin.

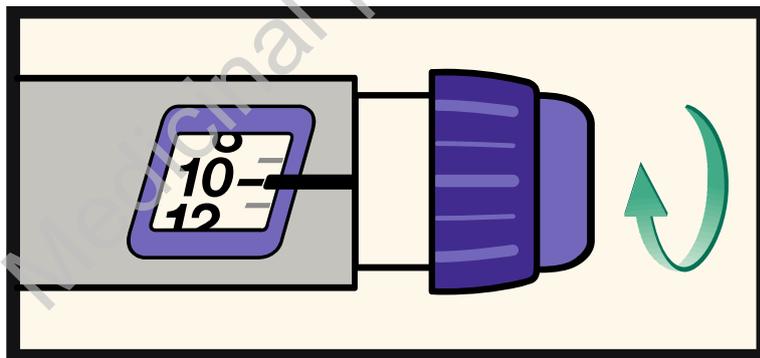
6. Select the dose

You can give from 1 to 60 units in a single injection. If the pen won't let you dial your full dose, there may not be enough insulin left in the pen. If you need to inject more than the number of units left in the pen, you may either:

- inject the amount left in your pen and then use a new pen to give the rest of your dose, **or**
- get a new pen and inject the full dose.

If you need help deciding how to divide your dose, ask your doctor or nurse.

Your dose number may be different than the one in this example. Follow the advice of your healthcare provider.



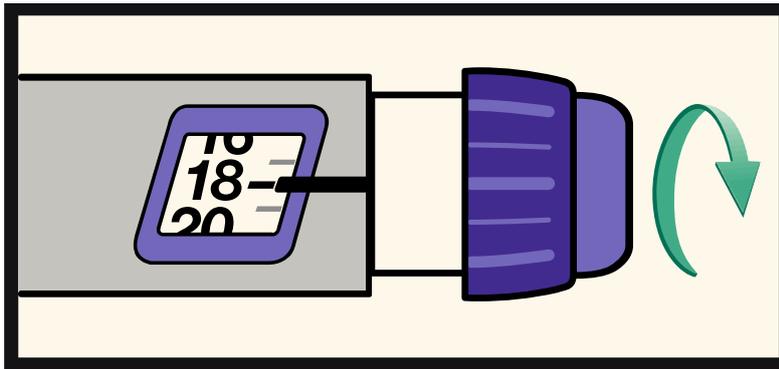
Dial your dose

Dial your dose by turning the dial until the correct number lines up with the black line on the window.

7. Check the dose

If you select the wrong dose.

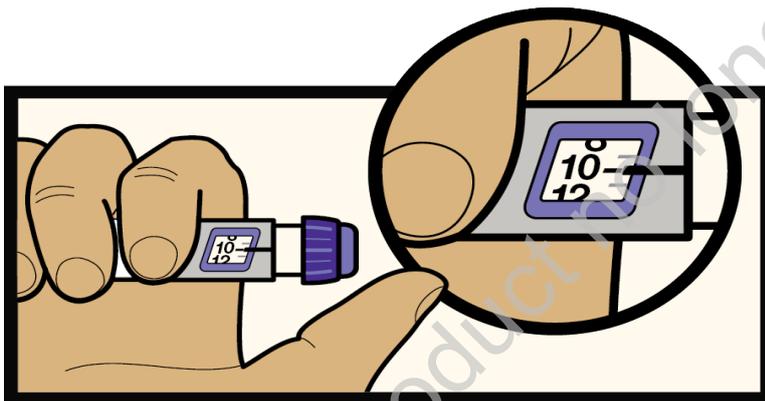
If you dial the wrong dose, just dial backwards until the correct number lines up with the black line on the window.



Double-check your dose!

It is very important that you dial the dose your healthcare provider recommended. Double-check that you set the right dose before injecting.

If you have not yet cleaned your injection site, do it now before you inject.



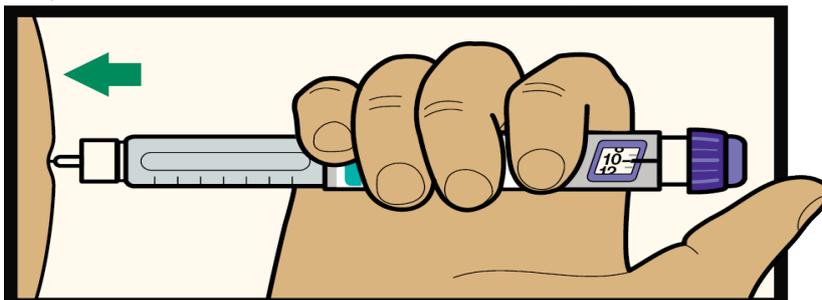
Check the dose window...

Before you inject, make sure that the dose window is facing you. You need to see the window clearly during the injection.

8. Give the injection

Insert the needle

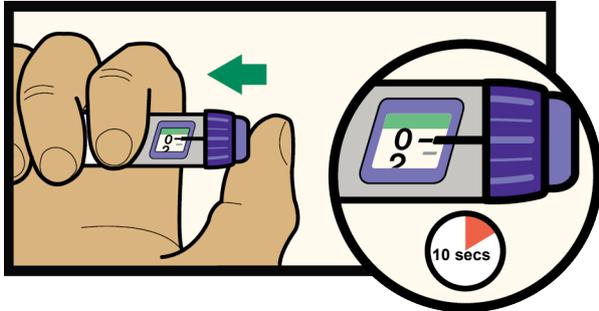
Simply insert the needle fully into the skin. Keep the pen straight, not at an angle or sideways.



Press to Inject

Deliver the dose by pressing the injection button until you see 0 and a green stripe appears in the window.

Count to 10 slowly after you see 0 and the green stripe.

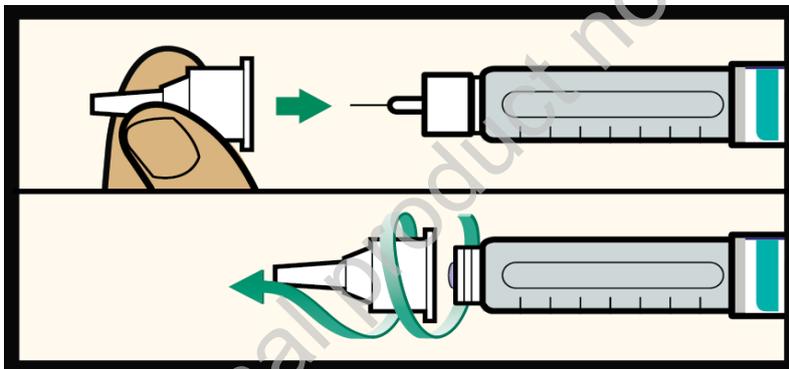


Counting to 10 allows time for all of the insulin to come out of the pen, making sure that you get your full dose.

9. After the injection

Be careful not to stick your finger with the needle.

Press outer needle cap on firmly and use it to unscrew the needle.

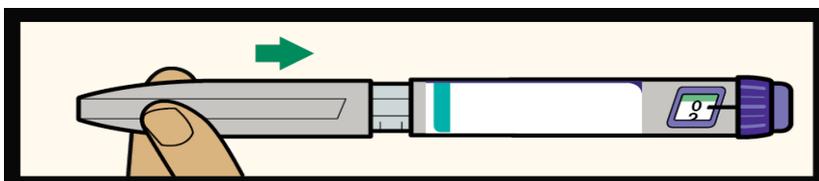


Put used needles in a closeable, puncture-resistant sharps container. Throw away the needle safely, as instructed by your doctor, pharmacist or nurse.

Do not reuse the needle; throw it away safely following the directions.

Storing your pen

Simply re-cap the pen, and store it without the needle for your next injection. For information on how to care for your pen, see section “Caring for your pen”.



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