ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Ondibta 100 units/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each pre-filled 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 in pre-filled pen (VitaClick)

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

Ondibta contains insulin glargine, an insulin analogue, and has a prolonged duration of action. Ondibta 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, Ondibta can also be given together with orally active antidiabetic medicinal products.

The potency of this medicinal product is stated in units. These units are exclusive to Ondibta 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
- Adolescents and children aged 2 years and older patients

The safety and efficacy of Ondibta in adolescents and children aged 2 years and older have been established (see section 5.1). The dose regimen (dose and timing) should be individually adjusted.
- Children below 2 years of age

The safety and efficacy of Ondibta have not been established. No data are available.

Switch from other insulins to Ondibta

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Ondibta, 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 Ondibta

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 Ondibta 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 Ondibta

Ondibta and insulin glargine 300 units/ml are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, 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 Ondibta 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 Ondibta.

Method of administration

Ondibta is administered subcutaneously.

Ondibta should not be administered intravenously. The prolonged duration of action of Ondibta 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 Ondibta. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Ondibta 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 Ondibta, the instructions for use included in the package leaflet 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

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.

Ondibta 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.

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, and dose adjustment of antidiabetic medications may be considered.

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 Ondibta, 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,
- 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

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).

Handling of Ondibta pre-filled pen

Ondibta 100 units/ml in pre-filled pen is only suitable for subcutaneous injections. Before using Ondibta, the instructions for use included in the package leaflet must be read carefully. Ondibta has to be used as recommended in these instructions for use (see section 6.6).

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 Ondibta 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 Ondibta 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 with known effect

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say 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 and sulfonamide 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 feto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity. The use of Ondibta 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 hyperglycemia. 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 breast-fed newborn/infant are anticipated since insulin glargine as a peptide is

digested into aminoacids 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 investigations are listed below by system organ class and in order of decreasing incidence (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; not known: cannot be estimated from the available data).

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

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
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			Cutaneous amyloidosis
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.

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

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.

Ondibta is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://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 Ondibta 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 halfmaximal 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 Ondibta therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

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,

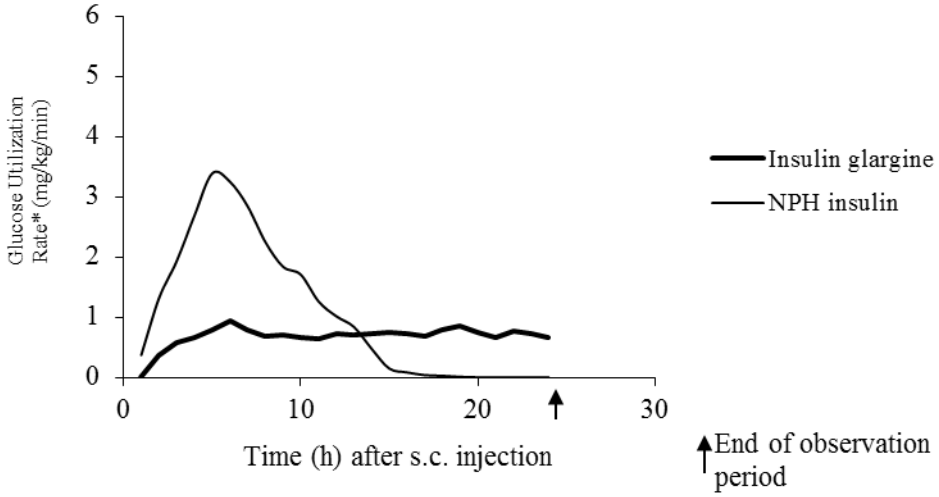
especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

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:

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.

Effects of insulin glargine (once daily) on diabetic retinopathy were evaluated in an open-label 5 year NPH-controlled study (NPH given bid) in 1 024 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 multicenter, 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 randomised (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 glycohemoglobin and the incidence of symptomatic hypoglycemia 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 hypoglycemic 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

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. The graph 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.

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

After subcutaneous injection of Ondibta in diabetic patients, insulin glargine is rapidly metabolized 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 Ondibta. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Ondibta 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 Ondibta.

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

3 years

Shelf-life after first use of the pen

The medicinal product may be stored for a maximum of 4 weeks not above 30 °C and away from direct heat or direct light.
The pre-filled 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

Not in-use Ondibta pre-filled pens

Store in a refrigerator (2 °C-8 °C).
Do not freeze or place next to the freezer compartment or a freezer pack.
Keep Ondibta pre-filled pen in the outer carton in order to protect from light.

In-use Ondibta pre-filled pens

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

6.5 Nature and contents of container

Type 1 colourless glass cartridge with a red plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (bromobutyl rubber and synthetic polyisoprene-EPDM blend) containing 3 ml of solution.
The cartridge is sealed in a disposable pen injector.
Needles are not included in the pack.

Packs of 1 and 5 Ondibta pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect Ondibta 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 Ondibta is a solution, it does not require resuspension before use.
Ondibta must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.
Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins (see section 4.4).

Ondibta 100 units/ml in pre-filled pen is only suitable for subcutaneous injections.
Before first use, the pre-filled pen must be stored at room temperature for 1 to 2 hours. Empty pre-filled 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.
Before using the pre-filled pen, the instructions for use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Gan & Lee Pharmaceuticals Europe GmbH, Prinzenallee 11a, 40549 Düsseldorf, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2000/001
EU/1/25/2000/002

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 https://www.ema.europa.eu

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

Gan & Lee Pharmaceuticals
No.8 Nanfeng West First Road
Huoxian Town
Tongzhou District
Beijing, China, 101109

Name and address of the manufacturer responsible for batch release

IL-CSM Clinical Supplies Management GmbH
Marie-Curie-Strasse 8
Loerrach, Baden-Wuerttemberg, 79539, Germany

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 (PSURs)**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ondibta 100 units/ml solution for injection in pre-filled pen
insulin glargine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 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) and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (VitaClick)
1 pen of 3 ml
5 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

OPEN HERE

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

Use only clear and colourless solutions.
Only use needles that are compatible for use with Ondibta.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened:
Store in a refrigerator.
Do not freeze or place next to the freezer or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In use conditions:
After its first use, the pen may be stored for a maximum of 4 weeks not above 30°C.
Do not refrigerate. Keep the pen protected 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

Gan & Lee Pharmaceuticals
Europe GmbH
40549 Düsseldorf
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2000/001 1 pen of 3 ml
EU/1/25/2000/002 5 pens of 3 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ondibta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Ondibta 100 units/ml solution for injection
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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ondibta 100 units/ml solution for injection in 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 Instructions for Use of Ondibta pre-filled pen, 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

What Ondibta is and what it is used for

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

Ondibta 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.

What you need to know before you use Ondibta

Do not use Ondibta

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

Warnings and precautions

Ondibta in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Ondibta.
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 box at the end of this leaflet).

Skin changes at the injection site

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Ondibta). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

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, needles 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 Ondibta in children below the age of 2 years.

Other medicines and Ondibta

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),
- sulfonamide 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 high blood pressure),
- 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 a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Ondibta 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 Ondibta

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

How to use Ondibta

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

Although Ondibta contains the same active substance as 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 Ondibta 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 Ondibta.

Ondibta 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 the box at the end of this leaflet for further information.

Use in children and adolescents

Ondibta 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 Ondibta every day, at the same time of the day.

Method of administration

Ondibta is injected under the skin. Do NOT inject Ondibta 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 Ondibta. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle Ondibta

Ondibta is a pre-filled disposable pen containing insulin glargine. Ondibta in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "Ondibta Instructions for Use" included in this package leaflet. 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 Ondibta (see “Ondibta Instructions for Use”).
A safety test must be performed before each injection.

Look at the cartridge before you use the pen. Do not use Ondibta if you notice particles in it. Only use Ondibta 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 Ondibta, consult your doctor, pharmacist or nurse.

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

Do not use Ondibta if it is damaged or not working properly, it has to be discarded and a new Ondibta has to be used.

Insulin mix-ups

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

If you use more Ondibta than you should

- If you **have injected too much Ondibta**, 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 box at the end of this leaflet.

If you forget to use Ondibta

- If you **have missed a dose of Ondibta** 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 box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Ondibta

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 Ondibta 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.

Possible side effects

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

If you notice signs of you blood sugar being too low (hypoglycaemia), take action to increase your blood sugar level straight away (see the box 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 pass out (become unconscious). Serious hypoglycaemia may cause brain damage and may be life-threatening. For more information, see the box 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 (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe allergic reactions to insulins may become life-threatening. Tell a doctor straight away if you notice signs of severe allergic reaction.

Skin changes at the injection site
If you inject insulin too often at the same place, the skin may either shrink (lipoatrophy) (*may affect up to 1 in 100 people*) or thicken (lipohypertrophy) (*may affect up to 1 in 10 people*). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

Common (may affect up to 1 in 10 people)
Skin and allergic reactions at the injection site
The 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 (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 (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.

How to store Ondibta

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 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 pens
Pre-filled pens in use or carried as a spare may be stored for a maximum of 4 weeks not above 30 °C and away from direct heat or direct light. The pen in use must not be stored in the refrigerator. Do not use it after this time period.

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.

Contents of the pack and other information
What Ondibta contains

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

What Ondibta looks like and contents of the pack

Ondibta 100 units/ml solution for injection in pre-filled pen is a clear and colourless solution. Each pen contains 3 ml of solution for injection (equivalent to 300 units).

Pack sizes of 1 and 5 pre-filled pens.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Gan & Lee Pharmaceuticals Europe GmbH, Prinzenallee 11a, 40549 Düsseldorf, Germany.

Manufacturer
IL-CSM Clinical Supplies Management GmbH Marie-Curie-Strasse 8 Loerrach, Baden-Wuerttemberg, 79539, Germany

This leaflet was last revised in

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

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 Ondibta").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, 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 Ondibta").

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 Ondibta 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 heart beat, 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 Ondibta,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Ondibta").

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 Ondibta 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.

INSTRUCTIONS FOR USE
Ondibta solution for injection in pre-filled pen

Ondibta is a pre-filled pen for the injection of insulin glargine. Your doctor has decided that Ondibta is appropriate for you based on your ability to handle Ondibta.

Talk with your doctor, pharmacist or nurse about proper injection technique before using Ondibta. People who are blind or have vision problems should not use the pen without help from a person trained to use Ondibta.

Read these instructions carefully before using your Ondibta. If you are not able to use Ondibta or follow all the instructions completely on your own, you must use Ondibta only if you have help from a person who is able to follow the instructions completely.

You can set doses from 1 to 60 units in steps of 1 unit. Each pen contains multiple doses. If your prescribed dose is more than 60 units, you will need to give yourself more than 1 injection.

Keep this leaflet for future reference.

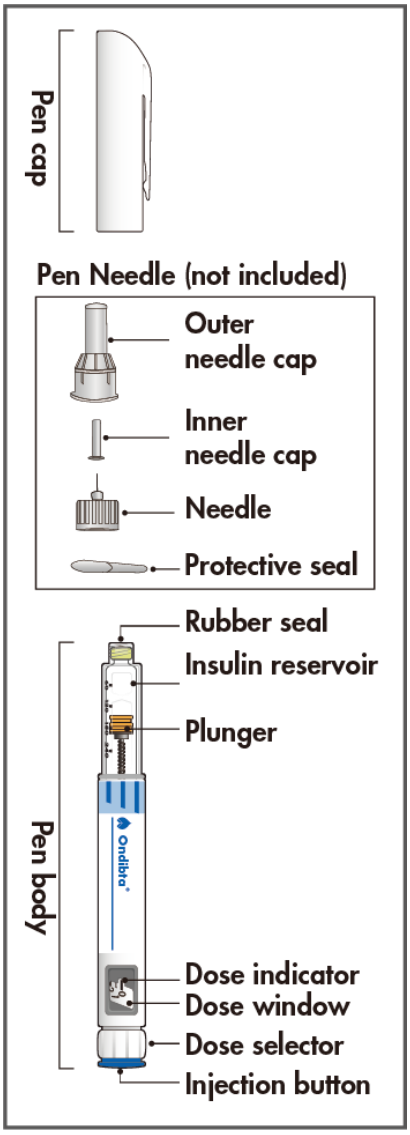


Figure A

Schematic diagram of the pen

Important information you need to know before injecting Ondibta

- If you use more than one type of insulin pen, **store the pens with different medicine in separate areas** and read the label of your pen before injecting.
- **Do not share your Ondibta with other people, even if the needle has been changed. This pen is only for your use.** You may give other people a serious infection, or get a serious infection from them.
- **Do not** use your pen, if it is damaged or if you are not sure that it is working properly. Be careful not to bend or damage the needle before use.
- **Do not** select a dose and/or press the injection button without a needle attached.
- **Do not** reuse needles. Always attach a new needle before each use. Only use needles that are compatible for use with Ondibta.
- 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.
- Always perform the safety test before each injection (see **Step 3**).
- Always have a spare pen and spare needles in case they get lost or damaged.

Need help?
If you have any questions about Ondibta or about diabetes, ask your doctor, pharmacist or nurse or call the local representative number on the front of this leaflet.

Materials needed

Make sure you have the following items:

Included in the carton

Ondibta solution for injection in pre-filled pen (see **Figure A**), containing a total of 300 units of insulin glargine.

Not included in the carton (to be obtained separately)

- New sterile needles with sizes compatible with this pen:
  – 31G, 5 mm
  – 32G, 4-6 mm
  – 33G, 4 mm
  – 34G, 4 mm
- Alcohol swab
- Sharps disposal container for used needles

Step 1. Check the pen and insulin

If your Ondibta pen is in the refrigerator, take it out 1 to 2 hours before you inject to allow it to reach room temperature (below 30°C). Injecting cold insulin can be uncomfortable.

A. Check the label on your Ondibta pen, to **make sure you have the correct insulin** (see **Figure B**) – this is especially important if you have other pens.
- Ondibta pen is white with a blue injection button.

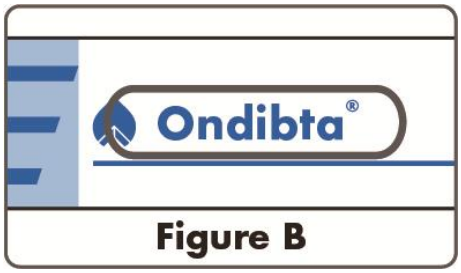


Figure B

B. Check the expiry date (EXP).
- **Do not** use your pen after the expiry date.

C. Pull off the pen cap.

D. Check the appearance of the insulin. Ondibta is a clear insulin.
- **Do not** use your pen, if the insulin is cloudy, coloured or contains visible particles.

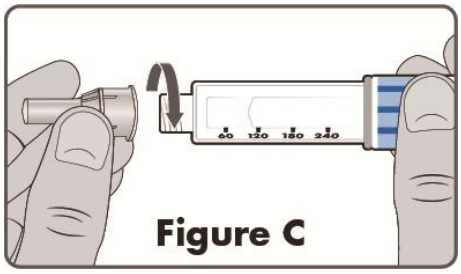
Step 2. Attach a new needle

Always use a new sterile needle for each injection. This helps prevent contamination and potential needle blocks.

A. Wipe the rubber seal with an alcohol swab.

B. Remove the protective seal from a new needle.

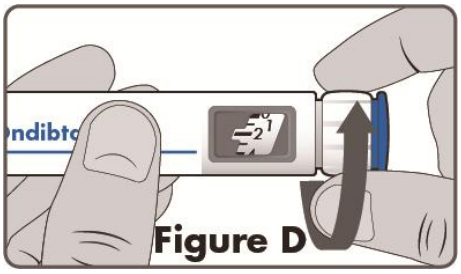
C. Keep the needle straight and screw it onto the pen until fixed (see **Figure C**).
- If the needle is not kept straight while you attach it, it can damage the rubber seal, cause the insulin to leak, or break the needle.



Step 3. Perform a safety test

Always perform a safety test before each injection to:
- make sure the pen and needle work properly.
- make sure you get the correct dose by removing air bubbles.

A. Select a dose of 2 units by turning the dose selector (see **Figure D**).
- If necessary, the selected dose can be corrected by turning the dose selector back down.



B. Pull off the outer needle cap (see **Figure E**) and keep it to remove the used needle after injection.

C. Pull off the inner needle cap (see **Figure E**) and discard it.

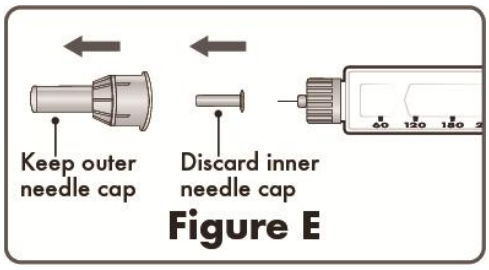


Figure E

D. Hold the pen with the needle pointing upwards. Tap the insulin reservoir (see **Figure F**) so that any air bubbles rise up towards the needle.

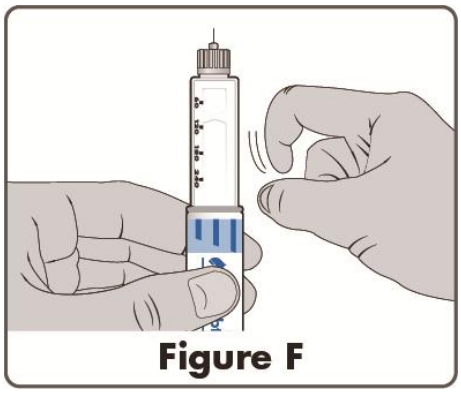


Figure F

E. Press the injection button all the way in (see **Figure G**).

- Check if insulin comes out of the needle tip. Your pen is working correctly if insulin comes out of the needle.

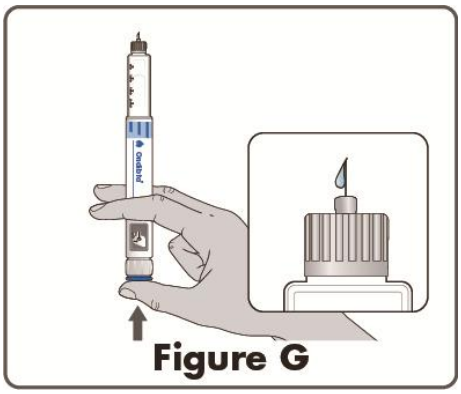


Figure G

You may have to perform the safety test several times before insulin comes out of the needle tip.

- If no insulin comes out of the needle tip, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and repeat the safety test.
- If no insulin comes out after changing the needle, your pen may be damaged. **Do not** use this pen.

Step 4. Select your dose

You can set the dose from 1 to 60 units in steps of 1 unit of insulin (one step equals 1 unit of insulin). If you need a dose greater than 60 units, you should give it as two or more injections.

A. Check that the dose window shows “0” following the safety test.

B. Select your required dose by turning the dose selector (see **Figure H**: selected dose is 30 units in this example).

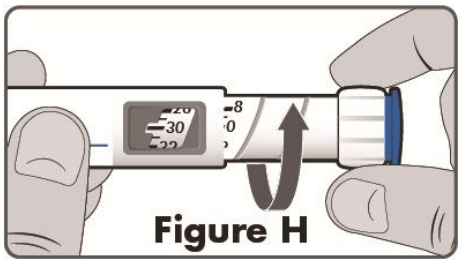


Figure H

- If you turn past your dose, you can turn back down.
- You will hear a click for every single unit dialed. **Do not** set the dose by counting the number of clicks you hear because you may get an incorrect dose.
- **Do not** push the injection button while turning, as insulin will come out.
- You cannot turn the dose selector past the number of units left in the pen.
- If the medicine left in the pen is less than your dose, inject what is remaining in the pen and complete your dose with a new pen, or use a new pen for your full dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale. **Do not** use this scale printed on the cartridge to measure your dose of insulin.

Step 5. Inject the dose

Use the injection method as instructed by your doctor, pharmacist or nurse.

A. Choose your injection site.

- The pen can be injected into your thigh, stomach area (abdomen) or upper arm (see **Figure I**).
- Change (rotate) your injection site for each injection.
- **Do not** inject where the skin has pits, is thickened or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard or into scars or damaged skin.

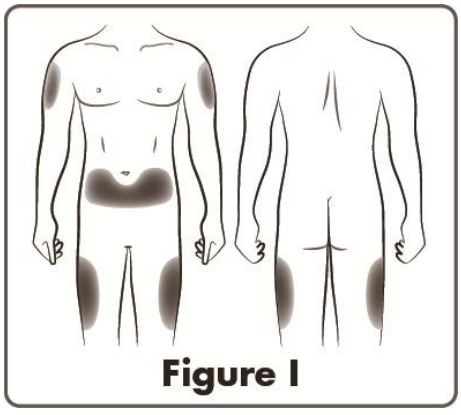


Figure I

B. Clean the injection site with an alcohol swab. Let it dry before injecting.

C. Insert the needle into the skin (see **Figure J)**.

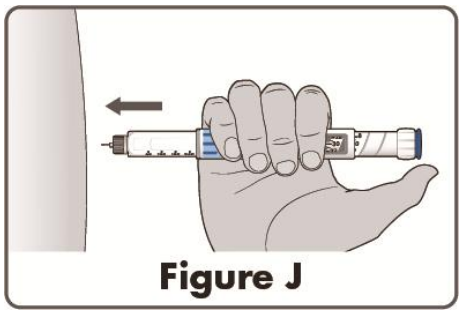


Figure J

D. Press the blue injection button all the way in to deliver the dose. The number in the dose window will return to "0" as you inject. **Do not** try to inject your insulin by turning the dose selector. You will not receive your insulin by turning the dose selector.

E. **Keep holding the blue injection button pressed all the way in. Slowly count to 10** (see **Figure K**) before you pull out the needle from the skin. This ensures that the full dose is given.

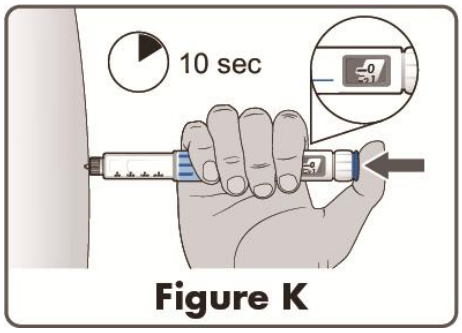


Figure K

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

If you find it hard to press the injection button in:

- **Do not** force it as this may break your pen.
- Change the needle (see **Step 6** and **Step 2**) and prime your pen (see **Step 3**).
- If you still find it hard to press in, get a new pen.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store the pen without a needle attached. This helps prevent:

- Contamination and/or infection.
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Carefully put the outer needle cap back on the needle (see **Figure L**), to reduce the risk of accidental needle injury.

- **Never** replace the inner needle cap.

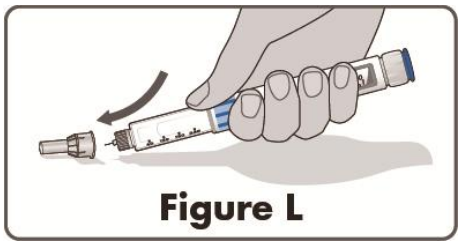


Figure L

B. Pinch the base of the outer needle cap to unscrew the used needle (See **Figure M**).

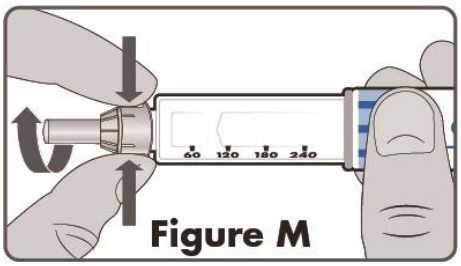


Figure M

C. Dispose of the needle safely, as instructed by your doctor, pharmacist or nurse.

D. Always put the pen cap back on. Store the pen until your next injection.

Storage instructions

Before first use

- Keep your pen in the refrigerator between 2 °C to 8 °C until first use.
- **Do not** freeze. Throw away your pen if it has been frozen.

After first use

- Store the pen you are currently using at room temperature below 30 °C, and away from light, dust and dirt.
- The pen in use must not be stored in a refrigerator.
- Once you take your pen out of the refrigerator, you can use it for up to 28 days. **Do not** use it after this time.
- **Do not** store your pen with the needle attached.
- **Keep your pen out of the reach and sight of children and any other persons who are not supposed to handle it.**
- When the pen is empty, throw it away without a needle on, as instructed by your doctor, pharmacist or nurse.

Maintenance

- You can clean the outside of your pen by wiping it with a damp cloth (water only).
- **Do not** soak, wash or lubricate the pen as this may damage it.
- Your pen should be handled with care. Avoid situations where the pen might be damaged. If you are concerned that your pen may be damaged, use a new one.