RISK MANAGEMENT PLAN FOR ONDIBTA

Risk Management Plan (RMP) version to be assessed as part of this application:

Invented Name	Ondibta (approved by the European Medicines Agency (EMA) on 14 December 2023)
Active substance(s) (INN or common name):	Insulin glargine
RMP Version number	0.2
Data lock point for this RMP	31 December 2022
Date of final sign-off	See signature page
Rationale for submitting an updated RMP	The updated RMP (Version 0.2) has been prepared in response to comments received as part of the D120 assessment for centralized procedure H0006136.
Summary of significant changes in this RMP	1.Update the invented name to Ondibta throughout the document. 2. Part 1 Product Overview – Updated "Indication(s)" as per SmPC section 4.1 of the reference product, in response to EMA's D120 request. 3.Updated the company address and phone of ProductLife Group. 4. Minor editorial changes for the clarification purpose.
Other RMP versions under evaluation	Not applicable.
Qualified Person for Pharmacovigilance (QPPV) name	Francesco Ventura On behalf of Applicant / Marketing Authorisation Holder: Gan & Lee Pharmaceuticals Europe GmbH
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder Gan & Lee Pharmaceuticals Europe GmbH' QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
ADR	Adverse Drug Reaction
ANSM	French National Agency for Medicines and Health Products Safety
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
DSUR	Development Safety Update Report
EMA	European Medicines Agency
FAR	Frequency of Adverse Reactions
FDA	Food and Drug Administration
HbA1c	Glycated Haemoglobin
HR	Hazard ratio
IBD	International Birth Date (Pharmacovigilance)
ICSR	Individual Case Safety Reports
IFU	Instructions for use (e.g. pen device)
IMP	Investigational medicinal product
INN	International Non-proprietary Name
MAH	Marketing Authorisation Holder
ORIGIN	Outcome Reduction with Initial Glargine Intervention
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information (US FDA) (equivalent of EU SmPC)
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics (EU)
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Events

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Insulin glargine
Pharmacotherapeutic group(s) (ATC Code)	Insulins and analogues for injection, long-acting (A10AE04)
Marketing Authorisation Holder	Applicant / Marketing Authorisation Holder: Gan & Lee Pharmaceuticals Europe GmbH Prinzenallee 11a, 40549 Düsseldorf, Germany
Medicinal product to which this RMP refers	FDA nomenclature: **Gan & Lee Insulin Glargine Injection, Solution** (100 units/ml, 3 ml cartridge) EMA nomenclature: **Gan & Lee Insulin Glargine 100 units/ml solution for injection in a cartridge** (3 ml), hereafter referred to by its invented name Ondibta
Invented name(s)	Ondibta (approved by the European Medicines Agency (EMA) on 14 December 2023)
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Insulin glargine is an Insulin analog. The chemical classification of insulin glargine is Insulin. Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$
	Summary of mode of action: Insulin glargine is a recombinant human insulin analogue produced by recombinant DNA technology with long-acting blood glucose lowering activity. Insulin glargine, like regular types of human insulin, regulates glucose metabolism by binding to insulin receptors on muscle and fat cells, thereby facilitating the cellular uptake of glucose. This lowers blood glucose levels. At the same time, insulin glargine inhibits the liver's conversion of stored glycogen into glucose, which also contributes to lower blood glucose levels. Insulin glargine also inhibits lipolysis in adipose tissue, inhibits proteolysis, and enhances protein synthesis (NCI05). (National Center for Biotechnology Information).
	Important information about its composition: Ondibta is a colorless, sterile solution presented in 3 mL cartridges for use. Each milliliter contains insulin glargine, glycerin, Metacresol, zinc chloride and water for injection. Insulin glargine is produced by recombinant DNA technology in *Escherichia coli* (K12 strain). Hydrochloric acid and/or sodium hydroxide are added for pH adjustment as required.
Hyperlink to the Product Information	Link to the latest approved (Applicants country specific and EU Lantus SmPC)

	EU Lantus Product Information: https://www.ema.europa.eu/en/medicines/human/EPAR/lantus#product-information-section Ondibta Product Information: Section 1.3.1 SmPC, Labelling and Package Leaflet
Indication(s)	The proposed indication is applied as per SmPC Section 4.1: Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.
Dosage	Current: Ondibta contains insulin glargine, an insulin analogue, and has a prolonged duration of action. Insulin Glargine Injection 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. 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.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: 3 mL (100 units/mL) sterile, and clear, colorless solution for subcutaneous injection in a cartridge.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring?	No.

ATC=Anatomical Therapeutic Chemical Classification; INN=International Non-proprietary Name; RMP=Risk Management Plan.

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Gan & Lee Insulin Glargine Injection, hereafter referred to as Ondibta, is a sterile, clear, colourless solution for subcutaneous injection indicated to improve glycemic control in adults and pediatric subjects with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

Diabetes is a chronic, progressive disease that, if inadequately treated, can lead to significant morbidity, including macrovascular and microvascular complications, and significantly increased mortality. In conjunction with ongoing patient lifestyle education regarding self-management of the disease, subcutaneous insulin is the mainstay of treatment for patients with T1DM and may be used to treat patients with T2DM.

T1DM characterized by autoimmune β-cell destruction, usually leading to absolute insulin deficiency, and T2DM (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance), are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Children with T1DM, the most common form of diabetes in the pediatric population, typically present with symptoms of polyuria/polydipsia, and approximately one-third present with diabetic ketoacidosis (DKA) [ADA 2020]. Occasionally patients with T2DM may present with DKA.

Diabetes is diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or Glycated haemoglobin (HbA1c) criteria [ADA 2020].

The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric-onset diabetes are different from adult diabetes. There are also differences in recommended care for children and adolescents with T1DM as opposed to T2DM.

In T1DM, consideration must be given to changes in insulin sensitivity related to physical growth and sexual maturation, the ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of DKA. In T2DM, lifestyle modifications, self-management of diabetes, and pharmacological medications play a pivotal role in its management.

Incidence and Prevalence:

From a global perspective, an estimated 26.9 million people of all ages equal to 8.2% of the U.S. population had diagnosed diabetes in 2018 (Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html). This total included 210,000 children and adolescents younger than 20 years of age, and of these approximately 187,000 had T1DM. During 2014-2015, the estimated annual number of newly diagnosed cases in the United States included 18,291 children and adolescents younger than 20 years of age with TIDM and 5,758 children and adolescents aged 10 to 19 years with T2DM.

In Europe according to a current metanalysis, the incidence of TIDM is 15 per 100 000 population, and the prevalence of TIDM is 12.2 per 10 000 people. (M Mobasseri et al, 2020)

The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014. An estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980 (Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes). The causes are complex, but the rise is due in part to increases in the number of people who are overweight, including an increase in obesity, and in a widespread lack of physical activity.

The main existing treatment options:

Diabetes of all types can lead to complications in many parts of the body and increase the risk of dying prematurely. It has been shown that a proportion of diabetes and its complications can be prevented by a healthy diet, regular physical activity, maintaining normal body weight and avoiding tobacco use.

Standard of care in developed countries includes lifestyle management, nutrition, pharmacologic approach (human insulin, insulin analogues, oral hypoglycemic agents, glucagon-like peptide receptor agonist, or bariatric surgery.

Important comorbidities

According to a WHO report, when diabetes is not treated or well managed, complications are life threatening. Acute complications contribute to mortality, and poor quality of life. People with diabetes are at greater risk of developing conditions such as cardiovascular disorders, neurological (nervous system) disorders, diabetic eye disease and kidney disease.

Severe hyperglycaemia may be life-threatening impact if it triggers DKA in T1DM and T2DM, and hyperosmolar coma in T2DM. Severe hypoglycaemia may result in seizures or loss of consciousness.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Chronic diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves, and increase the risk of heart disease and stroke. The result can be reduced blood flow, which – combined with neuropathy in the feet – which increases the chance of foot ulcers, infection and the eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long- term accumulated damage to the small blood vessels in the retina.

Diabetes is one of the leading causes of kidney failure. Uncontrolled diabetes in pregnancy can have a devastating effect on both mother and foetus, substantially increasing the risk of fetal loss, congenital malformations, stillbirth, perinatal death, obstetric complications, and maternal morbidity and mortality. Gestational diabetes increases the risk of some adverse outcomes for mother and offspring during pregnancy, childbirth and immediately after delivery such as high

blood pressure resulting in seizures during pregnancy. However, it is unknown what proportion of obstructed births or maternal and perinatal deaths can be attributed to hyperglycaemia. Due to increased life span, diabetes over long term has also been associated with increased rates of specific cancers, and increased rates of physical and cognitive disability.

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Toxicity

In 2015, a GLP-compliant, comparative evaluation of 28-day toxicity and toxicokinetic study S12581 was conducted. The study investigated the effects of repeated subcutaneous doses in Sprague-Dawley Rats of Ondibta, compared to US-sourced Lantus.

A total of 163 male and 163 female Sprague-Dawley rats were randomized into five groups in each portion, and received daily subcutaneous doses up to 27.5 U/kg, the no observable adverse effect level (NOAEL).

The toxicokinetic analysis showed that the systemic exposures (C_{max} and AUC_{last}) of insulin glargine and related metabolites (M1 and M2) were similar between Ondibta and Lantus. There were no apparent gender differences in the systemic exposures of insulin and related metabolites.

After 28-day of repeated subcutaneous dosing and a two-week recovery period, both Ondibta and Lantus elicited comparable immune responses in test-article treated rats. There were no insulin glargine antibodies detected in control animals in the main and recovery cohorts. There were three test-article related deaths, 2 were due to hypoglycemia and 1 could not recover from anesthesia. There were no adverse effects related to Ondibta or Lantus with respect to ophthalmology, hematology, coagulation, urinalysis, or organ weight parameters in the main or recovery animals after 4 weeks of once daily subcutaneous administration. Also, all groups of both genders exhibited comparable histopathological changes.

Therefore, all the data from multiple orthogonal functional studies are considered to assess functional and biological activities, the difference in insulin receptor Type A phosphorylation is unlikely to impact the safety or efficacy of the proposed biosimilar. Overall, findings with GL Glargine Injection and US Lantus do not preclude comparability. When compared with Lantus in Sprague-Dawley rats, GL Glargine Injection treatment was considered as safe as Lantus.

Safety pharmacology

Not applicable.

Other toxicity-related information or data

Not applicable.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Cumulative Subject Exposure in Clinical Trials

Clinical Studies Overview

The initial clinical studies of Ondibta were conducted in early product development for registration in China and the Far East before the regulatory pathway of biosimilarity was established on 28 February 2015.

Study GL070301R was a randomized, single-blind, crossover study conducted to compare the pharmacokinetic (PK) and pharmacodynamic (PD) properties of recombinant insulin glargine injection (Basalin) with Lantus and Novolin N. The study consisted of a three-period glucose clamp study of 16 healthy male subjects comparing Basalin with the Lantus and NPH insulin (Novolin N). The results indicate that Basalin or Lantus have more stable blood glucose lowering action and more stable serum insulin concentration than Novolin N.

Study IG-09-02 was a 24-week study which enrolled 278 patients with T2DM who were randomized 1:1 to GL Insulin Glargine or Lantus. The study demonstrated non-inferiority of recombinant insulin glargine (Basalin) compared to Lantus in the treatment of T2DM uncontrolled on oral antidiabetics. The efficacy and safety if recombinant insulin glargine (Basalin) is comparable to that of Lantus.

Study BJDB002R was a 12-week study designed to compare the efficacy and safety of the combination use of GL Insulin Glargine with glipizide GITS versus Novolin N with glipizide in patients with T2DM who were on oral anti-diabetic medications. The study employed a randomized, open-label, multi-center design and 471 subjects were randomized 3:1 to GL Insulin Glargine versus Novolin N. The results demonstrated that the success rate of HbA1c and FBG in insulin glargine group was better than ones in Novolin N group and Ondibta had a good safety and efficacy for diabetes mellitus.

Study GLARGINE 2012, was conducted to evaluate efficacy and safety of the GL Insulin Glargine, solution for injections 100U/ml in an open comparative randomized double cross-over multicenter clinical study in diabetes mellitus patients. A total of 72 patients were screened into the study, and of these 70 patients completed the study. The results of the study confirmed favourable tolerability and consistent safety and immunogenicity of insulin glargine treatment as compared to insulin Lantus.

Study KI/0513-3, an open-label, comparative, randomized, multicenter clinical study to compare the efficacy, safety and immunogenicity of Insulin Glargine and Lantus demonstrated the non-inferior efficacy of Gan & Lee insulin glargine to Lantus, over a 6-month treatment period in the treatment of patients with T1DM and patients with T2DM uncontrolled on oral hypoglycemic medications.

During the development of the proposed biosimilar insulin glargine, Gan & Lee has conducted four clinical studies in accordance with EMA and FDA regulatory requirements.

GL-GLA-001, a completed pilot, single dose, randomized, double-blind, 2-way crossover study provided indications that PD and PK effects of GL Glargine Injection will be bioequivalent to US-licensed Lantus in 47 patients with T1DM.

GL-GLA-CT1002, PK/PD similarity study, was an euglycemic glucose clamp trial investigating the PK and PD similarity of GL Glargine Injection to the US-licensed reference products (US-licensed Lantus) and EU-approved comparator product (EU-approved Lantus). The design was a randomized, double-blind, multicenter, single-dose, 3-way crossover, 3-treatment trial in male patients with T1DM. GL Glargine Injection demonstrated pharmacokinetic and pharmacodynamic similarities to both US-licensed Lantus and EU-approved Lantus, respectively.

Gan & Lee had conducted two additional studies, GL-GLAT1-3001 and GL-GLAT2-3002, to compare the immunogenicity, efficacy, and safety of GL Glargine Injection to EU-approved Lantus in adult patients with T1DM and T2DM, respectively. Immunogenicity, efficacy, and safety results from these two studies were similar between GL Glargine Injection and EU-approved Lantus.

Exposure During Clinical Trials 2003-2022

Up to 31-December-2022, 1,365 subjects have been enrolled and treated by Ondibta in clinical programs.

The estimated cumulative subject exposure from 18-Apr-2003 to 31-December-2022 is provided in Table 2.

Table 2 Cumulative subject exposure from clinical studies

Treatment	Approximate number of subjects
Gan &Lee Insulin Glargine Injection	1,365
Lantus**	1,015
Novolin (Isophane insulin)***	124
Novolin-N and glipizide#	118
Total	2,619

Source PBRER, 01-Jan-2022 to 31-Dec-2022

In the following tables, exposure by age group and gender (Table 3), gender (Table 4), and ethnic origin (Table 5) are provided.

Table 3 Cumulative Subject Exposure to Ondibta in Completed Clinical Studies by Age and Gender

Number of Subjects			
Age Range (Yr.)	**Male**	**Female**	**Total**
<18:	0	0	0
18 – 65:	419	173	592
66 – 75:	83	48	131
>75:	1	1	2
Missing:	0	0	0
Total=	503	222	725

[1]Data from the completed clinical studies GL-GLAT1-3001, GL-GLAT2-3002, GL-GLA-CT1002, GL-GLA -001 as of Data Lock Point (DLP) 31-December-2022. Source PBRER, 01-Jan-2022 to 31-Dec-2022

Data from some of the older completed studies (BJDB002R, IG-09-02, and KI/0513-3) (GL070301R; GLARGINE-2012,) was able to be retrieved only by gender. Table 4 includes exposure data across all studies including GL-GLA -001, GL-GLA-CT1002, GL-GLAT1-3001 and GL-GLAT2-3002 based on gender.

Table 4 Cumulative Subject Exposure to Ondibta from Clinical Studies by Gender

Number of Subjects			
Gender	**Male**	**Female**	**Total**
Ondibta from completed studies	834	531	1365

Table 5 Cumulative Subject Exposure to Ondibta from all Clinical Studies by Ethnic origin

Number of Subjects			
Ethnic origin	**Male**	**Female**	**Total**
Caucasian:	455	183	638
Black or African American:	28	23	51
Asian:	14	8	22
American Indian or Alaska Native:	1	2	3
Native Hawaiian or Other Pacific Islander:	2	2	4
Other:	1	2	3
Multiple:	2	2	4
Total	503	222	725

Table 6 Completed Clinical Studies in Support of EU and US Biosimilarity

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	FPFV[1]	Planned Enrollment	Subject Exposure**
GL-GLAT1-3001	III	US, Czech Republic, Germany, Hungary, Spain and Poland	An Open-label, Randomized, Multicenter, Phase III Study to Compare the Immunogenicity, Efficacy, and Safety of Ondibta to Lantus® (Insulin Glargine Injection) in Adult Subjects with Type 1 Diabetes Mellitus	Equivalence study to compare the immunogenicity, safety, and efficacy of Ondibta with that of the reference medicinal product, Lantus®, in adults with type 1 diabetes mellitus	Determined by the physician, according to the requirement of the subject	Subjects with T1DM who meet all the inclusion criteria and none of the exclusion criteria	31-Oct-2017	A total of 718 subjects with T1DM were screened for enrollment into this study.	Total number of subjects: 576 Of these 576 subjects, a total of 513 subjects (89.1%) completed the study.
GL-GLAT2-3002	III	US	An Open-label, Randomized, Multicenter, Phase III Study to Compare the Immunogenicity, Efficacy, and Safety of Ondibta to Lantus® (Insulin Glargine Injection) in Adult Subjects with Type 2 Diabetes Mellitus	Equivalence study to compare the immunogenicity, safety, and efficacy of Ondibta with that of the reference medicinal product, Lantus®, in adults with type 2 diabetes mellitus.	Determined by the physician, according to the requirement of the subject	Subjects with T2DM who meet all the inclusion criteria and none of the exclusion criteria	31-Oct-2017	A total of 802 subjects with T2DM were screened for enrollment into this study.	Total number of subjects: 567 Of these 567 subjects, a total of 515 subjects (90.8%) completed the study.

Table 6 Completed Clinical Studies in Support of EU and US Biosimilarity

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	FPFV[1]	Planned Enrollment	Subject Exposure**
GL-GLA-001	I	US	Exploratory, Randomized, Double-Blind, Two-Way Cross Over Study to Assess PK and PD Effects of Ondibta in Comparison to Lantus in Subjects With Type 1 Diabetes Mellitus	A pilot study to assess PK and PD effects of Ondibta in comparison to US-sourced Lantus	2 single 100 U/mL in 3 mL pre-filled pens dose administrations of GL Insulin Glargine, and US Lantus® by intervals of 7-10 days 0.4 IU/kg	T1DM	-	47 subjects assigned	Total number of subjects exposed: 47 (6 subjects dropped out of the study)
GL-GLA-CT1002	I	Germany	A glucose clamp trial investigating the biosimilarity of Ondibta (insulin glargine 100 U/mL) with US and EU Lantus® comparator products in patients with type 1 diabetes mellitus	A randomized, double-blind, multicenter, single-dose, 3-way crossover, 3-treatment, euglycemic glucose clamp trial in male subjects with type 1 diabetes mellitus	3 single 100 U/mL in 3 mL pre-filled pens dose administrations of GL Insulin Glargine, US Lantus® and EU Lantus® separated by intervals	Male subjects with T1DM as diagnosed clinically for ≥ 12 months	-	-	Total number of subjects: 113

Table 6 Completed Clinical Studies in Support of EU and US Biosimilarity

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	FPFV[1]	Planned Enrollment	Subject Exposure**
					of 5-21 days. Subjects were evenly allocated to one out of 6 sequences of single dose administrations of the 3 IMPs on 3 separate dosing visits.				

[1] First patient first visit (FPFV)

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Considered to be included as missing information: No

Rationale: The biosimilar phase 3 immunogenicity studies GL-GLAT1-3001 and GL-GLAT2-3002 are required by the EMA to enroll only a population as sensitive and homogeneous as possible to facilitate a maximum response and clear safety signals. Also, not all patient populations need be included.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency, or those caused by prolonged or cumulative exposure as it is designed to ascertain the equivalence of Ondibta to EU Lantus or US Lantus, and also determine if there are any differences in safety profile such as immunogenicity, hypoglycemia or serious adverse reactions (SARs) , or identification of any Suspected Unexpected Serious Adverse Reactions or new safety signals, or differences in efficacy (which would be a negative pharmacovigilance signal).

A biosimilar is not required by the EMA or FDA to re-establish the benefits of the protein, in this case glargine. Therefore, all patient populations are not studied but only those that constitute the most sensitive and homogeneous group, provide the best opportunity to detect any differences between the biosimilar candidate and the originator medicine.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	
Subpopulations carrying relevant genetic polymorphisms	
Pediatrics	

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Cumulative and Interval Patient Exposure from Marketing Experience

Ondibta is intended for use by diabetic patients, with the dosage and regimen individually adjusted by the health care provider depending on type (T1DM or T2DM), severity, weight, and age.

SV.1.1 Method used to calculate exposure (Patient Exposure)

An estimation was made on patient exposure to Ondibta marketed from 01 January 2012 to 31 December 2022.

The calculation used is based on a theoretical prediction, assuming that the average weight of all Chinese subjects is 60 kg, then the amount of Ondibta to be used is 0.3-0.4 U/kg per day, with an average daily use of 20 U.SV.1.2 Exposure

Cumulative global sales of GL Insulin Glargine since initial approval in China up to 31 Dec 2022 was [redacted] cartridges. Based on the above calculation, which equates 24 cartridges per person per year, an estimated exposure was calculated to be [redacted] patient-years.

Note: Since [redacted] of the total sales were outside of China, based on the average weight, actual exposure is likely to be varied.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

It is not expected the Ondibta has the potential for misuse for illegal purposes.

Overdose

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

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

More severe episodes of hypoglycemia, accompanied by coma, seizure, or neurologic impairment, may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary to prevent recurrence.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The comparability protocols demonstrated the biosimilarity of Ondibta to the reference product Lantus by means of physicochemical analyses, structural and impurity profile comparisons and biological analyses. This has been confirmed in clinical studies which indicate that Ondibta has a similar safety profile to the reference biological medicinal product. Data from clinical trials conducted by G&L were taken into account when determining the safety specification for this biosimilar product.

According to the evaluation made by Gan & Lee Pharmaceuticals of Ondibta, no new risk has been identified from the post-marketing experience of Ondibta marketed internationally outside of ICH countries. Therefore, the risks of Ondibta are considered as identical with that of Lantus.

The Lantus RMP includes important potential risk "Medication error" which is associated with insulin glargine 300units/mL, marketed by Sanofi-Aventis. As Gan & Lee has developed biosimilar to Lantus 100units/mL, this risk is excluded from the safety concerns for GL Insulin glargine.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

Risk-benefit impact: SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins

Potential mechanisms	Not relevant
Evidence source(s) and strength of evidence	Literature
Characterisation of the risk	**Frequency**: Literature: Often, two different insulin products with different onsets and durations of action are used concurrently to manage diabetes adequately. The common hypoglycemia. Based on data from two nationwide surveillance systems (National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance [NEISS-CADES] project and the U.S. Food and Drug Administration [FDA] Adverse Event Reporting System [FAERS]), among all Emergency Department (ED) visits for insulin errors between 2012–2017, approximately 60% reduction in the proportion of ED visits for insulin medication errors that involved mix-up errors (23.8% to 9.4%) was observed. Postmarketing data: To ~~data~~ date no cases of medication error due to mix up between long acting and short acting insulins have been reported. **Severity and nature of risk**: Hypoglycaemia, if left untreated, may be life-threatening or result in death. Postmarketing data: To ~~–~~date no cases of medication error due to mix up between long acting and short acting insulins have been reported. **Reversibility**: 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. **Background incidence/prevalence**: There is no information of the background incidence/prevalence of medication errors in patients treated with insulin glargine available in the literature.
Risk factors and risk groups	Visually impaired patients without help of a person trained for the use of the device

Preventability	Current prescribing information sufficiently describes all the necessary actions before or concomitantly the prescription and administration to prevent or minimize the appearance of the risk.
Impact on the risk-benefit balance of the product	No impact on the risk-benefit balance when the product is used in accordance with the label.
Public health impact	The evidence from literature and postmarketing data does not suggest any increased risk of medication error due to mix up of insulin glargine with other short acting insulins compared to other recombinant insulins.

Important potential risk: Malignancies	
Potential mechanisms	In vitro studies comparing insulin glargine and human insulin concluded that insulin glargine had a higher receptor affinity and mitogenic potency (Kurtzhals P, et al. 2000). However, the in vivo metabolism of insulin glargine in the blood suggests a low mitogenic potency due to the low affinity of its main metabolite for the IGF-1 receptor (Agin A, et al. 2007). Insulin is a growth factor, and it is possible that high levels of endogenous or administration of exogenous insulin could stimulate tumour growth. The potential oncogenic role of some insulin analogues (glargine in particular) has been suggested because of the known role in cellular reproduction of insulin-like growth factor (IGF-1) and insulin receptor signalling pathways. Insulin is both a metabolic hormone and a growth factor, same as cognate factor IGF-1. Cancer cells, overexpress the insulin receptor (IR) and, specifically, IR isoform A, may be more responsive to the mitogenic effect of insulin. High insulin levels also reduce IGF-1-binding proteins and increase free-IGF-1, overactivating the mitogenic effects of the IGF-1 pathway in tumour tissues. Moreover, in cancer cells, glargine and long-acting insulins have been shown to exert a greater proliferative effect relative to human insulin both through the IGF1 receptor and IR isoform A (Vicentini M, et al. 2022).
Evidence source(s) and strength of evidence	Literature
Characterisation of the risk	**Frequency:** The results of a French cohort study showed no increased risk of breast cancer was observed for glargine users compared with other basal insulins users, with a fully adjusted hazard ratio of 1.08 (0.72–1.62) (Fagot JP. 2013). Results from the CARING study, an observational study conducted in 5 countries (Denmark, Finland, Norway and Sweden and the UK)

Important potential risk: Malignancies	
	concluded no trend with cumulative treatment time for insulin glargine relative to human insulin was observed in risk for any of the ten studied cancer types (But, A, et al. 2017). A meta-analysis of 11 studies, showed no significant association between insulin glargine and prostate cancer, pancreatic cancer and respiratory tract cancer when compared with non-glargine insulin. Insulin glargine use was associated with lower odds of other site-specific cancer (Tang X, et al. 2012). For T1DM, evidence of an effect of insulin on cancer incidence is limited and variable. Cohort studies have shown a 10–37% increased risk for all cancers, but case-control studies have shown no association. Because these studies usually have a small sample size, they are not powered enough to explore site-specific cancer incidence. However, data suggest an increased risk for pancreatic, liver, and stomach cancer. These results are consistent with evidence from a large population-based study that included data from 5 national diabetes and cancer registries (Harding JL, et al. 2015). The ORIGIN trial investigators randomized 12,537 subjects with impaired glucose tolerance or type 2 diabetes to insulin glargine or standard care and examined cardiovascular outcomes and incidence of cancer. The investigators did not find an increased risk of cancer with the use of basal insulin glargine (hazard ratio for cancer, 1.00) (Gerstein HC, et al. 2012). **Severity and nature of risk:** Non-clinical data reveal no carcinogenic potential with insulin glargine. The severity of the risk varies based on the factors influencing the type of cancer. **Background incidence/prevalence:** A meta-analysis of all observational studies and randomized controlled trials evaluating the relationship of insulin glargine and cancer risk were identified in PubMed, Embase, Web of Science, Cochrane Library and the Chinese Biomedical Medical Literature Database, through March 2012. Odds ratios (ORs) with corresponding 95% confidence interval (CI) were calculated with a random-effects model. The analysis included 11 studies including 448,928 study subjects and 19,128 cancer patients were finally identified for the meta-analysis. Insulin glargine use was associated with a lower odds of cancer compared with non-glargine insulin use (OR 0.81, 95% CI 0.68 to 0.98, P=0.03; very low-quality evidence). Glargine did not increase the odds of breast cancer (OR 0.99, 95% CI 0.68 to 1.46, P=0.966; very low-quality evidence) (Tang X, et al. 2012).

Important potential risk: Malignancies	
	A retrospective cohort study based on data from the French National Health Insurance information system showed absolute event rates for all cancer in patients exposed to glargine versus other basal insulin users were 1,622 and 1,643 per 100,000 person-years, respectively. No significant association was observed between glargine exposure and overall cancer incidence after adjustment for sex, with a hazard ratio of 0.97 (95% CI 0.87, 1.07), or after additional adjustment for any other hypoglycemic agent use and duration of diabetes (Fagot JP. 2013). A study of a cohort of 19,337 incident insulin users from the Netherlands found a decreased risk for overall and colon cancer but no difference in risk for bladder, respiratory tract and prostate cancer, when comparing time-dependently defined cumulative time using insulin glargine to that using human insulin, though without further distinction between different treatment durations (Ruiter R, et al. 2012). A comparison of analogues with human insulin in the CARING five-country cohort study was conducted to assess the cancer risk among insulin users. National Health Registries from Denmark (1996–2010), Finland (1996–2011), Norway (2005–2010) and Sweden (2007–2012) and the UK Clinical Practice Research Datalink database (1987–2013) were used in this study. A total of 21,390 cancer cases occurred during a mean follow-up of 4.6 years. Of the 136 associations tested in the main analysis, only a few increased and decreased risks were found: among women, a higher risk was observed for colorectal (Reporting rate [RR] 1.54, 95% CI 1.06, 2.25) and endometrial cancer (RR 1.78, 95% CI 1.07, 2.94) for ≤0.5 years of treatment and for malignant melanoma for 2–3 years (RR 1.92, 95% CI 1.02, 3.61) and 4–5 years (RR 3.55, 95% CI 1.68, 7.47]); among men, a lower risk was observed for pancreatic cancer for 2–3 years (RR 0.34, 95% CI 0.17, 0.66) and for liver cancer for 3–4 years (RR 0.36, 95% CI 0.14, 0.94) and >6 years (RR 0.22, 95% CI 0.05, 0.92). No trend with cumulative treatment time for insulin glargine relative to human insulin was observed in risk for any of the ten studied cancer types (But, A, et al. 2017). A cohort study using Scotland-wide data of 4 years, showed that insulin glargine (n = 3,959) had the same incidence rate for all cancers as those not receiving insulin glargine (Hazard ration [HR] 1.02, 95% CI 0.77–1.36, p = 0.9 in the fixed cohort) The subset of patients using insulin glargine alone (n = 447) had a significantly higher incidence of all cancers than those using other insulins only (n = 32,295) (HR 1.55, 95% CI 1.01–2.37, p = 0.045), and those using insulin glargine with other insulins (n = 3,512) had a slightly lower incidence (HR 0.81, 95% CI 0.55–1.18, p = 0.26). Overall, insulin glargine use was not

Important potential risk: Malignancies	
	associated with an Increased risk of all cancers or site-specific cancers in Scotland over a 4-year time frame (Colhoun HM. 2009). The role of undiagnosed cancer on the likelihood of diabetes diagnosis has been suggested by evidence from a Danish population-based study; the study reported a higher cancer incidence rate ratio in the first year after diabetes diagnosis, which then decreased with diabetes duration. A similar trend was observed considering the start and duration of insulin therapy, with an incidence rate ratio starting at 5 and decreasing to 1.3 after 5 years of insulin treatment (Carstensen B, et al. 2012). **Impact on individual patient:** Due to lack of conclusive evidence from available literature, no association of the risk with insulin glargine could be established. The impact on individual varies depending on the various contributing factors.
Risk factors and risk groups	Several case-control studies and some meta-analyses indicate diabetes as a potential risk factor for the development of neuroendocrine tumours (NETs), especially for non-functioning tumours of pancreatic or gastric origin (Gallo M, et al. 2018). Evidence suggests that patients with cancer and diabetes have higher cancer-related mortality (Shahid RK, et al. 2021). The extrinsic factors including diet, the environment, and sugar compounds disrupt the gut microbial diversity and function, a phenomenon known as dysbiosis, and increase the risk of insulin resistance, diabetes and several types of gastrointestinal, hepatobiliary and head and neck cancers such as liver, pancreatic, esophageal, and most notably colorectal cancer. Underlying obesity associated with diabetes has cancer-promoting effects (Shahid RK, et al. 2021).
Preventability	Current prescribing information does not recommend any preventive measures to this risk as there has been no evidence for an excess risk for malignancy in patients treated with insulin glargine, till date.
Impact on the risk-benefit balance of the product	There is no impact on risk-benefit balance of the product due to this risk.
Public health impact	As there is no evidence for risk of malignancy in patients using insulin glargine the impact on public health remains undetermined.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

SVIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Medication errors due to mix-up between long-acting (basal) and short-acting (bolus)insulins
Important potential risks	• Malignancies
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Marketing Authorisation Holder (MAH) is committed to monitor all safety concerns during the post marketing utilization, to collect, and analyse Individual Case Safety Reports (ICSR) in order to detect signals and better quantify all potential safety concerns and missing information.

III.1 Routine pharmacovigilance activities

The routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for important identified risk of "medication error due to mix-up between long-acting (basal) and short acting (bolus) insulins":

These targeted follow-up questionnaires are used to monitor the events and gather additional safety information to better characterize the risks related to the use of insulin glargine.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the Summary of Product Characteristics (SmPC) of the reference medicinal product, EU sourced Lantus solution for injection in a cartridge.

V.1. Routine Risk Minimisation Measures

Table 7 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important Identified Risks	
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	**Routine risk communication:** *SmPC*: Section 4.2, 4.4 and 6.6 *PL*: Section 3 ***Routine risk minimization activities recommending specific clinical measures to address the risk:*** **SmPC:** Insulin Glargine must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation is included in Section 4.2. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins is included in Section 4.4 and 6.6. **PL:** Do not mix insulin glargine with any other insulins or medicines is included in Section 3. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Important Potential Risks	
Malignancies	**Routine risk communication:** *SmPC*: None *PL*: None ***Routine risk minimization activities recommending specific clinical measures to address the risk:*** **SmPC:** None

Table 7 Description of routine risk minimisation measures by safety concern

	PL: None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Missing information	
None	

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 8 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 6.6. PL Section 3. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up of ICSRs with structured forms Additional pharmacovigilance activities: None
Important Potential Risks		
Malignancies	Routine risk minimisation measures: None Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
NoneNone		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Ondibta (insulin glargine)

This is a summary of the risk management plan (RMP) for Ondibta. The RMP details important risks of Ondibta, how these risks can be minimised, and how more information will be obtained about Ondibta risks and uncertainties (missing information).

Ondibta's summary of product characteristics (SmPC) and its package leaflet gives essential information to healthcare professionals and patients on how Ondibta should be used.

Important new concerns or changes to the current ones will be included in updates of Ondibta RMP.

I. The medicine and what it is used for

Ondibta is authorised for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above (see SmPC for the full indication). It contains insulin glargine as the active substance, and it is given by subcutaneous injection.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ondibta, together with measures to minimise such risks and the proposed studies for learning more about Ondibta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet, and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ondibta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ondibta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ondibta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Medication errors due to mix-up between long-acting (basal) and short-acting (bolus) insulins
Important potential risks	• Malignancies
Missing information	• None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risks

Important identified risk: Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	
Evidence for linking the risk to the medicine	Literature
Risk factors and risk groups	Visually impaired patients without help of a person trained for the use of the device
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 6.6. PL Section 3. Additional risk minimisation measures: None

Important Potential Risks

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Literature
Risk factors and risk groups	Several case-control studies and some meta-analyses indicate diabetes as a potential risk factor for the development of neuroendocrine tumours (NETs), especially for non-functioning tumours of pancreatic or gastric origin (Gallo M, et al. 2018). Evidence suggests that patients with cancer and diabetes have higher cancer-related mortality (Shahid RK, et al. 2021). The extrinsic factors including diet, the environment, and sugar compounds disrupt the gut microbial diversity and function, a phenomenon known as dysbiosis, and increase the risk of insulin resistance, diabetes and several types of gastrointestinal, hepatobiliary and head and neck cancers such as liver, pancreatic, esophageal, and most notably colorectal cancer. Underlying obesity associated with diabetes has cancer-promoting effects (Shahid RK, et al. 2021).
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ondibta.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ondibta.

PART VII: ANNEXES

Table of Contents of Annexes

ANNEX–4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The specific adverse drug reaction follow-up form for the risk "Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins" is enclosed overleaf.

Global PV database number: _____
Global PTC number: _____
Date of follow-up contact: _____
Medical Device Information
Insulin 1 - _____
Method of delivery: ☐ Vial and syringe ☐ OptiClick ☐ Optiset
☐Optipen ☐Optipen Pro ☐Solostar ☐Autopen 24
Color of insulin pen (if using pen)- _____
Insulin 2 - _____
Method of delivery: ☐ Vial and syringe ☐ OptiClick ☐ Optiset
☐Optipen ☐ Optipen Pro ☐Solostar ☐Autopen 24
☐ Other - _____
Color of insulin pen (if using pen)- _____
Mix-up details
1. Please describe how the mix-up occurred.
_____
_____
_____.
2. Were any of the following felt to be factors in the occurrence of the mix-up? (check all that apply)
a. Similar color of pens/ cartridges/ vials ☐ Yes ☐ No
b. Other similarity in pens/ cartridges/ vials ☐ Yes ☐ No
i. Please describe- _____
c. Lack of attention at time of administration ☐ Yes ☐ No
d. Administered insulin in a hurry ☐ Yes ☐ No
e. Administered insulin in decreased lighting ☐ Yes ☐ No
f. Underlying visual impairment ☐ Yes ☐ No
If yes, please describe. _____
g. Color blindness ☐ Yes ☐ No
h. Difficulty reading label/insulin name on pen ☐ Yes ☐ No
i. Recent change in insulin/ pen/ cartridge/ vial ☐ Yes ☐ No
j. Using a single pen for 2 different insulin cartridges ☐ Yes ☐ No
k. Using identical pens (type and color) ☐ Yes ☐ No
l. Other _____

ANNEX–6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

There are no proposed additional risk minimisation activities with GL Insulin glargine.

ANNEX–7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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