Unit: Technical Assessment Unit

Public assessment report for biological products

Basalin 100 unit/ml

Administrative information:

Trade name of the medicinal product:	**Basalin® 100 unit/ml, solution for injection**
INN (or common name) of the active substance(s):	**Insulin glargine**
Manufacturer of the finished product	**Gan and Lee Pharmaceuticals No. 8 Nanfeng West 1st Street, Huoxian, Tongzhou District, Beijing 101109, China - CHINA.**
Marketing Authorization holder	**Gan and Lee Pharmaceuticals No. 8 Nanfeng West 1st Street, Huoxian, Tongzhou District, Beijing 101109, China - CHINA.**
Manufacturer responsible for secondary packaging and Batch Releaser	**Gyptopharma for pharmaceutical manufacturing and trading: plot 27- the industrial area in El khanka- Abu zaabal- beside El Nasr pharmaceutical chemicals company- El Khanka- El Qalyubia**
Applied Indication(s):	**Treatment of diabetes mellitus, adolescent and children aged 2 years and above**
Pharmaceutical form(s) and strength(s):	**Solution for injection** in a cartridge **100 unit/ml**
Route of administration	**S.C**
Registration track	**Normal Tracks**
Type of registration (EMA/FDA – Local)	**Imported**

List of abbreviations

AE: Adverse event
$AUC_{GIR.0-24h}$: area under the glucose infusion rate curve from 0 to 24 hours
AUC: Area under the curve
CI: Confidence interval
C_{max}: Maximum observed plasma concentration
DM: diabetes mellitus

DNA: Deoxyribonucleic acid
EU: European Union
EMA: European medicines agency
EU Lantus: Lantus® EU
GIR: Glucose infusion rate
GIR_{max}: maximum observed glucose infusion rate
GL glargine: Gan & Lee Insulin Glargine
GMP: Good manufacturing practice
HbA1c: N-(1-deoxy)-fructosyl-hemoglobin
IMP: Investigational medicinal product
IGI: Insulin glargine injection
LS: Least Squares
LS-mean: Least square mean
M1: Metabolite 1
MAH: Marketing Authorization Holder
NMPA: National Medical Products Administration
PD: Pharmacodynamic
PK: Pharmacokinetic

RLD: Reference listed drug
RP: Reference product
SC: Subcutaneous(ly)
T1DM: Type 1 diabetes mellitus
TEAE: treatment emergent adverse event
US Lantus: Lantus® US RLD
US: United States
WHO: World Health Organization

Table of contents

1. General introduction about the product including brief description of the Active Pharmaceutical Ingredient, its mode of action and indications

- The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism.
- Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis. The actions of insulin at the cellular level are initiated by insulin binding to its plasma membrane receptor.
- GL Glargine Injection is a sterile, clear and colorless solution for subcutaneous administration, supplied in a 3 mL Type I glass cartridge that is assembled into one pen device presented as a disposable, variable-dose, multiple-dose pre-filled pen.
- GL Glargine Injection is developed as a proposed biosimilar product to Lantus, the reference product.
- Lantus is manufactured by Sanofi-Aventis and has been authorized under Marketing Authorization Number EU/1/00/134/001-004 (June 2000) in the European Union (EU

2. Quality aspects:

Introduction

As mentioned in the aforementioned section.

Drug Substance (Active ingredient)

- **General information**

-International non–proprietary name (INN): Insulin glargine
- Insulin glargine is a human insulin analogue that consists of two chains. The A-chain is composed of 21 amino acid residues, and the B-chain is composed of 32 amino acid residues. Its primary structure is identical to that of human insulin except that position 21 in the A-chain is Gly rather than Asn and there are two additional arginine amino acid residues at the C-terminal of the B-chain, Arg (B31) and Arg (B32).

- **Physicochemical Characterization**

- The drug substance is White or almost white powder, Soluble in dilute mineral acids. Practically insoluble in water and in anhydrous ethanol and Isoelectric point is approximately 7.0.

- **Biological characterization**

- Insulin glargine and its reference product, Lantus (approved insulin glargine product), were equipotent in in-vitro metabolic and mitogenic assays; and had the same in vitro binding characteristics and affinity for insulin receptor and IGF-1 receptors.

- **Manufacture, process controls and characterization:**

➢ **Manufacturer**:

- The drug substance is manufactured & controlled at No.8, Nanfeng West First Road, Huoxian, Tongzhou District, Beijing, 101109, China
- The site complies with the GMP requirements.

➢ **Description of Manufacturing Process and Process Controls**

- Gan & Lee insulin glargine is produced by recombinant DNA technology.
- The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.
- The manufacturing process of insulin glargine drug substance includes fermentation, cell harvest and disruption, inclusion body concentrate preparation, refolding, trypsin digestion, purification, crystallization and freeze drying, packaging, labeling, storage and release.
- The steps of each process are described in details.

➢ **Control of Materials**

- All materials for production are purchased from qualified suppliers. All materials received with the manufacturer's Certificate of Analysis (CoA)
- List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided.
- Information regarding the used cell line & cell banking is mentioned in detail in the MA file.
- Based on adventitious agents' safety evaluation, the risk of contamination with adventitious agents is low.
- No materials of animal origin are used in the manufacture of drug substances, thus eliminating the risk of exposure to Transmissible Spongiform Encephalopathy (TSE)/Bovine Spongiform Encephalopathy (BSE).

➢ **Controls of Critical Steps and Intermediates**

- Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart.
- The process controls selected for each critical manufacturing step and justification of the proposed acceptance criteria are provided in the MA file.

➢ **Process Validation**

- All manufacturing processes have been qualified in accordance with approved protocols and evaluated in the reports.
- The process performance qualification was carried out on three consecutive batches based on factory practice and process experience using the proposed commercial process and controls.
- The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.

➢ **Manufacturing Process Development**

- The developmental history of the manufacturing process is sufficiently describing the whole changes made to the DS manufacturing process with proper justification.
- Detailed description for each step development is mentioned in the MA file.
- Relevant information on drug substance batches manufactured during development, in relation to the change, is provided in the MA file.
- Process characterization overview of insulin Glargine is provided in the MA file.

➢ **Characterization**

- Details of primary secondary and high order structure, post translation forms, biological activity, purity and immunochemical properties are provided in the MA file.
- The structure (primary structure and higher order structure), other physicochemical characteristics and in vitro biological activity of insulin glargine have been established.
- The analytical techniques used for structure and biological activity characterization are
- provided in the MA file.
- Samples and reference standard batch numbers used in the Characterization Studies are provided in the MA file.
- Analysis results of process related impurities and product related impurities in the DS from three PPQ lots are provided. All results are within the mentioned acceptance limits.
- The nitrosamine risk assessment is provided in the MA file.

➢ **Specification**

- The tests performed on the drug substance comply with the requirements of ICH Q6B guideline, USP, Ph. Eur, and In-house practices.
- Detailed SOPs are provided with their validation report.

- The identity, purity, potency, physicochemical properties & microbiology of DS are tested.
- The specification change history for insulin glargine drug substance is provided in the MA file.

➢ **Batch analysis**

- For batch analysis, DS lots used in non-clinical study, clinical study or with clinical process, stability studies, justification of specification, and process performance qualification (PPQ) were chosen.
- Batches qualified against EU specification and used for setting proposed commercial DS.
- Three consecutive PPQ batches are used for batch analysis and found to meet specifications.
- Batch analysis results are confirmed to proposed specifications.

➢ **Reference Standards or Materials**

- The information provided regarding reference standards was sufficient, with the applicant submitting testing, specifications, and qualification protocols for both primary and working standards. These were accompanied by their certificates of analysis (COAs) and traceability to the primary standard, along with characterizations.

➢ **Container closure system**

- Gan & Lee Insulin glargine drug substance (DS) is packed into a container closure system consisting of polypropylene copolymer (PPCO) bottles and polypropylene (PP) caps. An all-aluminum bag is used to pack the bottle to protect from dust and light.
- The container closure system provides adequate protection from light, moisture, and microbial contamination to the DS for at least 36 months at -25℃ to -18℃.

➢ **Stability of drug substance**

- Based on available stability data

✓ **Approved Shelf Life:**
36 months

✓ **Approved Storage Conditions:**
-20 ± 5℃

Drug product:

➢ **Description and Composition of the Drug Product:**

- Insulin Glargine Injection (Gan & Lee insulin glargine injection) is a sterile, clear and colorless solution supplied in a 3 mL Type I glass cartridge that is assembled into a pen

device, presented as a disposable, variable-dose, multiple-dose pre-filled pen. It is a combination product intended for self-administration via subcutaneous injection.
- The drug product composition has been fully detailed, including the active substance and accompanying excipients along with their respective functions.
- Each cartridge is overfilled to contain not less than 3.3 mL (3.3 g) insulin glargine drug product.
- The components of the container closure system of Gan & Lee insulin glargine injection are provided in MA file.

Pharmaceutical Development

➢ **Components of drug product**

- Insulin glargine drug substance (DS) from Gan & Lee is produced through recombinant DNA technology using a genetic engineered strain of Escherichia coli as the expression host cell.
- The excipients and their final quantities are the same as those in the reference product (EU-licensed Lantus). No new excipients are introduced in the Gan & Lee drug product compared to the reference product.

➢ **Formulation Development**

- Gan & Lee insulin glargine injection is formulated as a clear, colorless, and sterile solution for subcutaneous injection with an active ingredient content at 100 units/mL corresponding to 3.64 mg/mL of insulin glargine.
- The composition of Gan & Lee insulin glargine injection (finished drug product) is selected based on the published available information of the reference product Lantus® (insulin glargine injection) for subcutaneous injection.
- There is no overage in the formulation of Gan & Lee insulin glargine injection

➢ **Manufacturing Process Development**

- Development of compounding and filling process is provided in MA file.
- Process Parameter Risk Assessment is well performed.
- Process Parameters and In Process Controls is well discussed in MA file.
- Process Material Compatibility Study is performed.
- Development of Pen Assembly, Labelling, and Packaging Process is provided in MA file.

➢ **Microbiological Attributes**

- Insulin glargine injection is a sterile product that is manufactured using an aseptic process. The microbiological control strategy of insulin glargine injection is provided in MA file.
- Summary of microbial testing including (hold-time study for low endotoxin recovery, container closure integrity (dye penetration method) is well illustrated.

- **Compatibility**

- For the compatibility of the drug product and primary packing materials which directly contact with injection including cartridge, plunger, and stopper.
- The in-use stability studies indicate that product quality remains qualified during 28-day in-use practice, thus, the compatibility of the needle with the insulin glargine injection was confirmed.

Manufacture of the drug product:
Description of manufacturing process and process controls along with manufacturers and responsibilities.

- **Manufacture**:
  - Manufacturer of the finished product is No.8, Nanfeng West First Road, Huoxian, Tongzhou District, Beijing, 101109, China.
  - The proposed size of commercial batch and list of all components of the dosage form to be used in the manufacturing process and their amounts on a per batch basis is provided.
  - Processing and hold times have been defined for the various steps in the manufacturing process from DS thawing to packaging of the final product based on validation.

- **Control of critical steps and intermediates**
  - Controls of Critical Steps and Intermediates including tests and acceptance criteria are provided and they ensure that the process is controlled.

- **Process validation and / or evaluation**
  - Description and results of process validation and Overview of process performance qualification are provided in MA file.
  - Hold time validation & Sterilization of components, parts and equipment is performed.
  - Procedures and Specification for Aseptic Process Validation are provided.
  - Validation of the Sterilizing Filters is performed.
  - The OOSs and deviations occurred during the PPQ are summarized in MA file.
  - Continued Process Verification is provided.

- **Product specification:**
  - Specifications proposed for release and shelf-life testing of the finished product comply with current ICH guidelines Q6B /USP/Eur.Ph.
  - Detailed SOPs validation protocols & reports are provided for the in-house methods
  - The provided Certificates of Analysis (COAs) comply with the stated specifications.
  - Justification of the drug product specifications at the release and during stability studies are provided.

- **Reference Standards or Materials.**
  - The reference standard used for release and stability testing of Basalin100 unit /ml is the same as the reference standard used for insulin glargine DS.

- **Container closure system**

-Insulin glargine injection is supplied in a filled and sealed glass cartridge, which is assembled in a disposable pen injector. The cartridge, rubber stopper, and aluminum cap/rubber seal constitute the primary container closure system

The disposable pen injector (device component) consists of three sub-assemblies:

- dosing mechanism
- cartridge holder
- pen cap

- **Stability of the drug product**

- Based on available stability data,
  - ✓ **Approved Shelf Life:**
    36 months
  - ✓ **Approved Storage Conditions:**
    <u>Unopened cartridges:</u>
  - Store in a refrigerator (2 - 8°C).
  - Do not freeze or place next to the freezer compartment or a freezer pack.
  - Keep the cartridge in the outer carton in order to protect from light.

    <u>Shelf-life after first use of the cartridge:</u>
  - The medicinal product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
  - The cartridges in use must not be stored in the refrigerator.

3. Non –clinical aspect:

- Basalin® or GL insulin glargine injection (IGI), is a basal (long-acting) human insulin analog produced by recombinant DNA technology and is being developed as a proposed biosimilar to Lantus® (insulin glargine injection, manufactured by Sanofi-Aventis). It is indicated for the treatment of DM in adults, adolescents and children aged 2 years and above. Basalin® has received production approval and GMP certificate from the China NMPA (National Medical Products Administration) in 2005.

- **Pharmacology:** The comparative in vitro pharmacology studies were conducted to characterize the receptor binding potency, functional activity, and three metabolic activities (glucose uptake, lipogenesis, and glycogen formation) between IGI, and EU Lantus®. Differences were observed in IR-A phosphorylation capability and glucose uptake activity while there were no differences observed in target binding and the other two metabolic assay (glycogen synthesis

and lipogenesis) results between IGI, and EU Lantus®. Given all the data from these studies, these differences observed are unlikely to impact the safety or efficacy of the proposed biosimilar.

- **Pharmacokinetics:** Based on the results of the PK analysis, it was concluded that the systemic exposures (AUC & C_{max}) of insulin and related metabolites (M1 and M2) were similar between IGI and Lantus® and showed no apparent gender differences. Overall, the assessment of functional & biological activities and systemic exposure of insulin and its related metabolites (M1 and M2) for IGI and Lantus® at doses of up to 27.5 U/kg/day does not preclude comparability.
- **Toxicology:** IGI or Lantus® given to rats up to 27.5 U/kg/day for 4 weeks via SC injection resulted in no observable adverse effects with respect to ophthalmology, hematology, coagulation, urinalysis, or organ weight parameters in all study groups. There were reduced glucose levels at all dose levels. Test article-related early deaths occurred in three animals but with no abnormal gross necropsy findings, therefore they were considered due to hypoglycemia. These findings were comparable between IGI or US Lantus® and consistent with the pharmacological action of both products. A comparable number of main and recovery animals developed serum ADAs after treatment with IGI or Lantus®. A 2-week recovery period following treatment phase resulted in non-adverse, reversible findings at all dose levels. Considering the human equivalent dose of the dose levels used in this study is much higher than the dose used in IGI phase 1 study and actual dose levels in practice, the findings observed in this study are likely to be an exaggerated effect of high exposure.
- **Overall conclusion:** Overall, findings with IGI and EU Lantus® do not preclude comparability. The biosimilar comparability exercise is considered satisfactory, and no safety issues were identified.

4. Clinical aspect:

Gan & Lee Insulin Glargine Injection (hereafter referred to as GL Glargine Injection), developed by Gan & Lee Pharmaceuticals for the Marketing Authorization Holder (MAH), as a proposed biosimilar to Lantus® (insulin glargine injection for subcutaneous injection; hereafter referred to as Lantus). The active ingredient of GL Glargine Injection has the same amino acid sequence as the active ingredient of Lantus.

Gan & Lee has conducted 4 studies with GL Glargine Injection to compare PK, PD, immunogenicity, safety, and efficacy to Lantus. In addition to the clinical studies conducted by the Applicant, the Applicant relied on the established clinical efficacy and safety data of Lantus.

➢ **Clinical Pharmacology:**

- GL Glargine injection demonstrated both pharmacokinetic and pharmacodynamic similarities to US Lantus and EU Lantus.
- Based on the primary and secondary PK endpoints in Phase I pivotal PK/PD similarity study **(GL-GLA-CT1002)** of the insulin glargine metabolite M1, Gan & Lee Insulin Glargine was similar to Lantus® US RLD and to Lantus® EU RP, since the 90% CI of the respective geometric LS-mean treatment ratio lay within the limits of 80.00 to 125.00%.
- Based on the primary PD endpoints $AUC_{GIR.0-24h}$ and $GIR_{max,}$ Gan & Lee Insulin Glargine was similar to Lantus® US RLD or Lantus® EU RP, since the 90% CI of the respective LS-mean treatment ratio of untransformed data lay within the limits of 80.00 to 120.00%. The similarity was also supported by the 90% CI of the LS-mean treatment ratio of log-transformed data which lay within the limits of 80.00 to 125.00%.

➢ **Clinical Efficacy:**

- **Results of studies** (GL-GLAT1-3001) and (GL-GLAT2-3002) **demonstrated** therapeutic equivalence and noninferiority of GL Glargine Injection compared to EU Lantus with respect to efficacy.
- **According to WHO Guidelines on evaluation of biosimilars "**An adequately powered comparative efficacy and safety trial **will not be necessary** if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise".
- **According to EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues** "There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins".

➢ **Clinical Safety:**

- Based on Phase I Pivotal study **(GL-GLA-CT1002)**, Gan & Lee Insulin Glargine, Lantus® US RLD and Lantus® EU RP were **well-tolerated** and safe at single SC doses of 0.5 U/kg, when administered to male subjects with T1DM.
- There were no clinically relevant differences between the AE profiles of the 3 IMPs with the majority of AEs being moderate in intensity and equally distributed.
- While anti-insulin antibody status had an effect on PK results, there was no clear difference in PD results between subjects with and without positive anti-insulin antibodies.
- **For studies (GL-GLAT1-3001) and (GL-GLAT2-3002),** during the 26-week treatment period, Overall, the incidence of AEs was consistent with treatment expectations, and no new safety signals were identified. The overall percentage of subjects with any TEAE, the proportions of subjects experiencing TEAEs overall and the most common TEAEs were **similar** in the GL Glargine Injection and EU Lantus treatment groups. No clinically

meaningful differences were found in the safety outcomes between the GL Glargine Injection and EU Lantus treatment groups.

- **Clinical Immunogenicity:**

- Based on the results of studies **(GL-GLAT1-3001) and (GL-GLAT2-3002) in which the primary objective** was to evaluate **equivalence of GL Glargine Injection and EU Lantus in terms of immunogenicity** there were no clinically meaningful differences between the GL Glargine Injection and EU Lantus treatment groups in terms of immunogenicity.
- **According to WHO Guidelines on evaluation of biosimilars "**for well-characterized biological substances (insulin), where an extensive literature and clinical experience indicate that immunogenicity **does not impact upon product safety and efficacy, immunogenicity studies may not be necessary** provided that the biosimilar is highly similar to the RP and the risk-based evaluation indicates a low risk**".**
- **According to EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues "**Safety studies should be performed with specific focus on immunogenicity and that the potential impact of anti-drug antibodies, if detected, on glycemic control, insulin requirements and safety, especially local and systemic hypersensitivity reactions, should be investigated**"**, the data submitted by the applicant was in agreement with this guideline.

- **Benefit/ Risk discussion:** In conclusion the overall benefit/risk of Basalin 100 unit/ml solution for injection is favorable in treatment of DM in adults, adolescents and children aged 2 years and above.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.