EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Glargivin

Date: November 2024

Unit: Technical Assessment Unit

Assessment report
Glargivin

Administrative information:

Invented name of the medicinal product:	Glargivin 100 u/ml
INN (or common name) of the active substance(s):	INSULIN GLARGINE 100 u/ml ;
Marketing Authorization holder	Eva Pharma for Pharmaceutical Industries (2) , Polaris Industrial District, Plot No. 27, North extensions area, 6th of October City, Giza
Applied Indication(s):	Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above
Pharmaceutical form(s) and strength(s):	- Solution for injection - 100 u/ml
Route of administration	Subcutaneous injection

List of abbreviations

- **AE**: adverse event
- **ALT**: alanine aminotransferase
- **AST**: aspartate aminotransferase
- **AUC**: area under the plasma concentration-time curve
- **AUC0-t**: area under the plasma concentration-time curve from time 0 to the last quantifiable time point
- **AUC0-inf**: area under the plasma concentration-time curve from time 0 to infinity
- **BUN**: blood urea nitrogen
- **CBC**: complete blood count
- **CI**: confidence interval
- **DBP**: diastolic blood pressure
- **DVT:** deep vein thrombosis
- **ECG**: electrocardiogram
- **Emax**: maximal activity
- **FDA**: Food and Drug Administration
- **GCP**: Good Clinical Practice
- **h or hr**: hour(s)
- **HBsAg**: hepatitis B surface antigen

- **HCV**: hepatitis C virus
- **HIV**: human immunodeficiency virus
- **IC**: informed consent
- **ICH**: International Conference on Harmonization
- **IRB**: Institutional Review Board
- **kg**: kilogram(s)
- **L**: liter
- **LMWHs**: Low Molecular Weight Heparins
- **Ln**: natural logarithm
- **mg**: milligram(s)
- **mL**: milliliter(s)
- **ng**: nanogram(s)
- **OTC**: over-the-counter
- **PD**: pharmacodynamic
- **R**: reference formulation
- **RBC**: red blood cell
- **SAE**: serious adverse event
- **SBP**: systolic blood pressure
- **T**: test formulation
- **T-R, R-T:**Test -reference , reference -test
- **tmax**: time to maximum activity
- **t½:** half-life
- **WBC**: white blood cell

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 25.8.2024 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

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

Glargivin Solution for Injection is a second brand product developed by Eva Pharma for Pharmaceutical Industries (2) for reference product Abasaglar solution for injection, Eli Lilly. The active ingredient of the product is Insulin Glargine (recombinant DNA origin); Insulin glargine is a modified form of human insulin to treat adults and children with type 1 diabetes and adults with type 2 diabetes to improve and maintain glycemic control. Insulin glargine is a long-acting insulin injected once daily and provided a basal insulin level throughout the day. They are used in one fill volume 3 ml Cartridges.

The pharmaceutical development of this product was straight forward depending on the data provided by Eli Lilly

About the product

-Glargivin belongs to recombinant DNA origin used in the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

2. Quality aspects:

Drug Substance (Active ingredient): Referred to MA of Abasaglar

2.2.3 Drug product:

-Description and Composition of the Drug Product:

Material Name	Quantity [Per 1 ml solution]	Unit
Active ingredient(s)		
Insulin Glargine * (Recombinant DNA origin) equivalent to 100 Units	3.6377	mg
Inactive ingredients		
Metacresol	2.70	mg
Glycerin	17.0	mg
Zinc oxide	QS	mg
Hydrochloric acid	QS	mg
Sodium Hydroxide	QS	mg
Water for injections	QS to 1.0	ml

- Pharmaceutical Development

Components of drug product

The excipients used in Glargivin Solution for Injection are Metacresol, Glycerin Zinc oxide, Hydrochloric acid, Sodium hydroxide and Water for Injections. The excipients used in the development of formulation are present in the reference product Abasaglar solution for injection, Eli Lilly.

- Formulation Development

The composition of the drug product was selected to match exactly the formulation of the reference products Quantitively and Qualitatively. No own formulation development was performed but followed the reference product formulation.

- Physicochemical and Biological Properties

The pharmaceutical development of this product was straight forward depending on the data provided by Eli Lilly

- Manufacturing Process Development

the process development could be more streamlined. A process was set up, where the manufacture of Glargivin drug product includes dispensing materials, dissolving the active pharmaceutical ingredient (API) and excipients, adjusting the pH, and performing sterile filtration. In parallel,

cartridges undergo washing, siliconization, and depyrogenation. Once prepared, the filling process begins, followed by packaging.

- **Microbiological Attributes**

- The antimicrobial effectiveness test & container closure integrity tests were performed and meet the USP requirement, Sterility test and Endotoxin testing were conducted on three batches.

- **Compatibility**

The product glargivin has filled into Primary container: Transparent glass cartridges (Type I), with chlorobutyl plunger on one side and Combiseal (Aluminum cap + Chlorobutyl) On the other side. The compatibility of the solution for injection with the immediate packaging material is monitored in the stability studies.

- **Manufacture of the drug product:**

Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer:

-The finished product manufacturing and batch release take place at Evapharma for Pharmaceutical Industries (2), Polaris Industrial District, Plot No. 27, North extensions area, 6th of October City, Giza

-The manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.

- The manufacturing method consists of several stages, namely: dispensing, preparation of solution containing the API and excipients with the desired pH, filtration and filling of solution in cartridges that were siliconized and depyrogenated followed by packaging

- Control of critical steps and intermediates

The critical steps of Glargivin drug product manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- Process validation and / or evaluation

All the mentioned in-house tests were validated and met the criteria & the pharmacopeial methods were verified

- **Product specification:**

-The specifications proposed for release and stability testing of glargivin finished product comply with Ph. Eur. and in-house based on Eli Lilly

-The specifications include appearance, general tests, tests for identity, tests for purity/product-related impurities, activity, quantity, tests for contaminants.

- Justification of the drug product specifications at the release and during stability studies are provided.

- Excipients specification & analysis are according to their respective monograph in the current edition of the European Pharmacopoeia or USP Current edition, except for some additional specifications for Glycerol, Metacresol and Zinc oxide (microbial limit test & endotoxin test).

-These components are controlled and tested to the standards appropriate for their intended use and function.
-no further impurities are introduced during the drug product manufacturing process.

- **Reference Standards or Materials.**

The reference standard is used to serve for release and stability assays for both drug substance and drug product.

- **Container closure system**

Glargivin Solution for Injection is supplied as Transparent PVC/Alu blister containing, transparent glass cartridge (Type I), with chlorobutyl plunger on one side and Combiseal (Aluminum cap + Chlorobutyl) on the other side, inside a carton box with suitable dimensions with patient information insert leaflet. Primary container: Transparent glass cartridge made of glass type I, with chlorobutyl plunger on one side and Combiseal (Aluminum cap + Chlorobutyl) on the other side

Secondary container: Transparent PVC/Alu blister of dimensions of 11 cm x 9.5 cm inside Carton box of dimensions of 11.5 cm x 9 cm x 2.5 cm.

Non –clinical and Clinical aspects:

The development, characterization and manufacture of Glargivin Solution for Injection have been adequately described. The manufacturing process is described in sufficient details and has been satisfactorily validated. The IPC tests are described and deemed suitable for controlling and monitoring the manufacturing process. The results indicate that the finished product can be reproducibly manufactured.
As a second brand for Abasaglar 100IU, the comparability study was reviewed according to ICH Q5E & successfully demonstrated that there is no statistically significant difference between Abasaglar and Glargivin Solution for Injection.
No major quality aspects impacting Glargivin Solution for Injection
Thus, No need for preclinical and clinical evaluation

Benefit/ Risk discussion:

In conclusion the overall benefit/risk assessment of Glargivin is favorable in the Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.