**Unit: Technical Assessment Unit**

# Public assessment report for biological products

***Humaxin Rapid***

## Administrative information:

| | |
|---|---|
| Trade name of the medicinal product: | Humaxin Rapid 100 u/ml |
| INN (or common name) of the active substance(s): | Insulin human100 u/ml |
| Manufacturer of the finished product | Evapharma for Pharmaceutical Industries (2) , Polaris Industrial District, Plot No. 27, North extensions area, 6th of October City, Giza - EGYPT ; (Line under construction) |
| Marketing Authorization holder | Evapharma 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<br>- 100 u/ml |
| Route of administration | Subcutaneous injection |
| Registration track | Normal track |
| Type of registration (EMA/FDA – Local) | Local |

## 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 Harmonisation
- **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

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5. Benefit/risk conclusion……...

6. General Conclusion and Recommendations if any……..

**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 30.9.2024 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**

Humaxin Rapid Solution for Injection is a second brand product developed by Eva Pharma for Pharmaceutical Industries (2) as a second brand product for reference product Humulin R Injection, Eli Lilly. The active ingredient of the product is Human Insulin (recombinant DNA origin); it is insulin is a 2-chain peptide having the structure of the antidiabetic hormone produced by the human pancreas. The primary activity is the regulation of glucose metabolism. Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. They are used in one fill volume 3 ml Cartridges.

**About the product**

-Humaxin Rapid 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)**

Drug substance part is not assessed as it was previously approved in MA file of Humulin R 100IU

**2.2.3 Drug product:**

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

Clear colorless solution, inside transparent glass cartridges (Type I), with chlorobutyl plunger on one side and Combiseal (Aluminum cap + Chlorobutyl) on the other side. Composition of the dosage form:

*Table (3.2.P.1.A) Composition*

| Material Name | Quantity [Per 1 ml solution] | Unit | % | Reference | Function |
|---|---|---|---|---|---|
| Active ingredient(s) | | | | | |
| Human Insulin* (Recombinant DNA Origin) equivalent to 100 IU | 3.5 | mg | 0.35 | Ph. Eur. 11 (0838)/ USP 2023 | API |
| Inactive ingredients | | | | | |
| Metacresol | 2.5 | mg | 0.25 | Ph. Eur. 11 (2077)/ USP 2023 | Preservative |
| Glycerol | 16.0 | mg | 1.60 | Ph. Eur. 11 (0496)/ USP 2023 | Tonicity modifier |
| Hydrochloric acid | QS | mg | - | Ph. Eur. 11 (0002) / USP 2023 | pH adjustment |
| Sodium Hydroxide | QS | mg | - | Ph. Eur. 11 (0677)/ USP 2023 | pH adjustment |
| Water for injection --- to ---- | 1.0 | ml | 97.80 | Ph. Eur. 11 (0169)/ USP 2023 | Vehicle |

**- Pharmaceutical Development**

**Components of drug product**

Humaxin Rapid Solution for Injection is a second brand product developed by Eva Pharma for reference product Humulin R Injection, Eli Lilly. The active ingredient of the product is Human Insulin (recombinant DNAorigin); having the structure of the antidiabetic hormone produced by the human pancreas. The primary activity is the regulation of glucose metabolism. Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production.

**- Formulation Development**

The composition of the drug product was selected to match exactly the formulation of the reference products. 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 Humaxin Rapid 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 and meet the Ph. Eur. requirements

**- Compatibility**

- Humaxin Rapid Solution for Injection contains Human Insulin as the active ingredient. All the ingredients that are part of the finished product are commonly used excipients. The excipients

used in Humaxin Rapid Solution for Injection are Metacresol, Glycerol, Hydrochloric acid, Sodium hydroxide and water for injection. The excipients used in the development of formulation are present in the reference product Humulin R Injection, Eli Lilly.

*No new excipients were tried in this second brand product. Considering the stability information of the marketed products and the development strategy, there was no significance for doing the excipient compatibility study.*

**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 Eva pharma 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 Humaxin Rapid 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 Humaxin Rapid finished product comply with Ph. Eur. and in-House.

-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 USP, except for some additional specifications for Glycerol& Metacresol (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**

Humaxin Rapid 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 aspect:**

**Clinical aspects**

The development, characterization and manufacture of Humaxin rapid 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 Humulin R 100IU, the comparability study was reviewed according to ICH Q5E & successfully demonstrated that there is no statistically significant difference between Humulin R 100IU and Humaxin rapid Solution for Injection.
No major quality aspects impacting Humaxin Rapid Solution for Injection
Thus, No need for preclinical and clinical evaluation