Unit: Technical Assessment Unit

Public assessment report for biological products

Humaxin mix 70/30

Administrative information:

Trade name of the medicinal product:	Humaxin mix 70/30
INN (or common name) of the active substance(s):	Soluble human insulin 30% / human insulin isophane (NPH) 70% 100 I.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
Marketing Authorization holder	Evapharma for Pharmaceutical Industries (2) , Polaris Industrial District, Plot No. 27, North extensions area, 6th of October City, Giza - EGYPT
Applied Indication(s):	Anti-diabetic
Pharmaceutical form(s) and strength(s):	Suspension for SC injection 100 I.U./ml
Route of administration	SC injection
Type of registration (EMA/FDA – Local)	Local

List of abbreviations

S.C.	Subcutaneous
MA	Marketing Authorization
IPC	In process control
GMP	Good manufacturing practice
USP	United states pharmacopeia
U/KG	Unit /Kilogram
BP	British pharmacopeia
CPP	Critical process parameter
SOPs	Standard operating procedures
NPH insulin	neutral protamine Hagedorn insulin
EDQM	European Directorate for the Quality of Medicines & HealthCare
PVC/Alu	Aluminium Polyvinyl chloride

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

Humaxin mix 70/30 Suspension for Injection is a second brand product developed by Eva Pharma for Pharmaceutical Industries (2) as a second brand for reference product Humulin 70/30 Suspension for Injection, Eli Lilly. The active ingredient of the product is Human Insulin; Human 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.
The pharmaceutical development of this product was straight forward depending on the data provided by Eli Lilly.

2. Quality aspects:

2.2.1 Introduction:
as mentioned above in the general introduction.

2.2.2 Drug Substance (Active ingredient)

Drug substance part is not assessed as it was previously approved in MA file of **Humulin 70/30 Suspension**.

2.2.3 Drug product:

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

-the product is composed of Human insulin (recombinant DNA origin) as the main active ingredients & Metacresol (preservative), glycerol (tonicity modifier), liquified phenol (preservative), protamine sulfate (complexing agent), dibasic sodium phosphate (buffering agent), zinc oxide (stabilizer), hydrochloric acid & sodium hydroxide (pH adjustment)
All of them are compendial.

- **Pharmaceutical Development including brief description on** Components of drug product.

-Human Insulin is used as active ingredient in Humaxin mix 70/30 Suspension for Injection. Human Insulin is procured from Eli Lilly which is White or almost white powder.

-The excipients used in the development of formulation are present in the reference product Humulin 70/30 Suspension for 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.

- Excipients are selected based on the reference product, Humulin 70/30 Suspension for Injection, Eli Lilly. All inactive ingredients used in the formulation are standard pharmaceutical substances complying with pharmacopeial monographs.

- **Formulation Development**

-The aim of the formulation development was to develop a formulation of Humaxin mix 70 / 30 Suspension for Injection that is equivalent to the reference product Humulin 70/30 Suspension for Injection, Eli Lilly. Both reference and test products showed similar behavior in physical and chemical characteristics.

-A comparative study has been performed. This comparative study involves the comparison of the results obtained by the analytical testing of sample of the production scale up of Humaxin mix 70/30 Suspension for Injection against a sample of a commercial batch of Humulin 70/30 Suspension for Injection. The results are match closely and the deviation is negligible. Therefore, it can be concluded that Humaxin mix 70/30 Suspension for Injection is essentially similar to the reference product Humulin 70/30 Suspension for Injection.

- The impurities in the finished product had their origin from the active pharmaceutical ingredient, Human Insulin

- **Overages**

-The quantity of Human Insulin includes a 1 % excess to guarantee a final concentration of 100 IU / ml.

- **Physicochemical and Biological Properties**

*Human Insulin is White or almost white powder.

*The chemical formula: $C_{257}H_{383}N_{65}O_{77}S_{6}$.

*the molecular weight: 5808 g/mol.

*PH Value:

- The control of the pH value of the injectable solution is determined conductometrically according to Ph. Eur. Method.

- The pH value of the finished product is controlled as **IPC** during the preparation of the active solution and during the batch release of the finished product.
*Particulate matter: The control method is performed according to the methodology provided by USP and Ph. Eur. 2.9.19.

- **Manufacturing Process Development.**

-All manufacturing steps and procedures have been performed following the latest GMP regulations.
-detailed description of the development is well mentioned in the MA file.

- **Container closure system and their compatibility.**

-Primary container: Transparent glass cartridges (Type I), with chlorobutyl plunger on one side and Combiseal (Aluminum cap + Chlorobutyl) on the other side with glass beads contained in the cartridge to facilitate resuspension.
-regarding compatibility of material of construction and dosage form, the product showed no change in physical appearance and insignificant change in chemical properties during 6 Months stability, thus confirming the compatibility of packaging material with the finished product. As for the performance, kindly note that compatibility of device with Humaxin Mix Cartridges is studied.

- **Microbiological Attributes.**

-Humaxin mix 70/30 Suspension for Injection is a **sterile product**. The finished product is supplied in **multiple-dose** Cartridges, and it is only opened prior to administration. Thus, the sterility of the product can be assured.
-Bacterial endotoxins limit has been established based on the maximum dose of Human Insulin (6.25 U/KG).
-Antimicrobial effectiveness test as per USP.
-regarding the integrity of container closure system to prevent microbial contamination, as per USP <1207> Package Integrity Evaluation, integrity of container closure is assessed through Container closure integrity test performed during process validation

- **Manufacture of the drug product:**

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

-the product is manufactured, packaged & released at Evapharma for pharmaceutical industries (2).

- **Manufacturing process:**

-narrative description & flow diagram of the process is well illustrated in the MA file showing the preparation of the solution (insulin section, buffer section & Insulin Section 100U/ml) followed by filtration & circulation procedures followed by mixing and filling
-CPP are showed up on the flow diagram.
-the steps are controlled through various IPCs

- **Control of critical steps and intermediates**

-the CPPs are mentioned in the MA file with their limits.

- **Process validation and / or evaluation:**

-Process validation has been performed for three consecutive production batches of Humaxin mix 70/30 Suspension for Injection. All equipment and procedures involved in the manufacturing of validation batches are the same as those used for normal production batches

- **Product specification:**

-some specifications proposed for release and stability testing of the finished product comply with European, BP, USP & In-house based on Eli Lilly.
-Detailed SOPs validation protocols & reports are provided.
-The specifications include physical & chemical characters and microbiological examination of the drug product.
- All the mentioned in-house tests were validated and met the criteria & the pharmacopoeial methods were verified.
-Justification of the drug product specifications at the release and during stability studies are provided.
-the used excipients are pharmacopeial.
-no excipient is found to be of human or animal origin or novel excipient.

- **Reference Standards or Materials.**

-list of references were provided in the MA file with their corresponding potency and use.

- The reference standard for Human Insulin was procured from EDQM.
- The reference standards for Insulin Porcine for system suitability was procured from EDQM.
- The reference standard for Metacresol was procured from the USP.
- The reference standard for Zinc oxide was procured from Merck.
- The reference standard for Phenol was procured from the USP

- **Container closure system.**

-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 with glass beads contained in the cartridge to facilitate resuspension.
-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.
-the specification for each component is provided in the MA file.

- **Stability of the drug product.**

-Based on available stability data

- **approved Shelf Life:**
  -24 months

- **approved Storage Conditions:**
  -Store in a refrigerator at temperature (2-8°C)
  -Do not freeze
  -Do not expose to excessive heat or direct sunlight.
- In-use storage conditions (after cartridge insertion):
  -Store in room temperature with shelf life 28 days (below 30 °C)

Adventitious agents:
NA

3. **& 4. Non –clinical aspect & Clinical aspect:**

The development, characterization and manufacture of Humaxin Mix 70/30 Suspension 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 70/30 Suspension for Injection, the comparability study was reviewed according to ICH Q5E & successfully demonstrated that there is no statistically significant difference between Humulin and Humaxin Mix Suspension for Injection.
No major quality aspects impacting Humaxin Mix Suspension for Injection
Thus, No need for preclinical and clinical evaluation

5. **General Conclusion and Recommendations if any:**

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