TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR 4-EPEEDO-10 (EPIRUBICIN HYDROCHLORIDE 10MG/VIAL) LYOPHILIZED INJECTION

Version number 1.0

14TH APRIL, 2022

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1. Introduction

4-EPEEDO-10 is a generic medicine of Ellence or Pharmorubicin (Epirubicin hydrochloride 2 mg/ml) Solution for Injection or Infusion of Pfizer. 4-EPEEDO-10 is an anticancer medicine belonging to Antineoplastic agents, Anthracyclines and related substances group. 4-EPEEDO-10 exerts is activity by binding to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary lung, prostatic and ovarian carcinomas). 4-EPEEDO-10 is approved in Tanzania for use in adults

1.1 Product details

Registration number	TZ 19 H 0124
Brand name	4-EPEEDO-10
Generic name, strength and form	Epirubicin hydrochloride 2 mg/ml) Lyophilized Injection
ATC classification	ATC code: L01DB03 Antineoplastic agents, Anthracyclines and related substances
Distribution category	POM
Country of origin	INDIA
Associated product	NA
Marketing Authorization Holder	Naprod Life sciences Pvt. Ltd, Tarapur Industrial area, Boisar, Dist; Thane-401506, Maharashtra, INDIA
Local Technical Representative	Jilichem(T)Ltd Pharmaceutical & Surgical Wholesale, Nyerere Road, block B-2, Opp Super Doll, Behind Victoria Complex (Lifemate Furniture), P O Box 22400, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of 4-EPEEDO-10 was submitted on 23rd June 2017. The product underwent full assessment. Assessment was completed in 3 rounds of evaluation 4-EPEEDO-10 was registered on 15th May 2019

1.3 Information for users

Visual description of the finished product	Orange red coloured lyophilized mass

Primary packing material	5 ml 20mm flint tubular flint vial plugged with 20mm rubber stopper sealed and 20mm flip off aluminium seal
Secondary packing materials	Cardboard carton box
Shelf-life and storage condition	24 months, Store between 15°C and 30°C. Protect from light
Route of administration	For IV use
Therapeutic indications	Epirubicin has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma. Intravesical administration of Pharmorubicin has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is <POM, the package insert contains full prescribing information as per SmPC

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: 4-EPEEDO-10

Composition: Epirubicin hydrochloride 2 mg/ml, Lactose Monohydrate, Methyl paraben, Hydrochloric acid, Sodium Hydroxide and Water for Injection

Pack size: 1 x 5 mL vial

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store between 15ºC and 30ºC. Protect from light

Manufacturer address: Naprod Life sciences Pvt. Ltd., Tarapur Industrial are, Boisar, Dist. Thane-401 505, Maharashtra, India.

Unique identifier: NA

Special warnings/precautions or instructions for use: Cytotoxic agents

The details of the primary pack include:

Brand name and strength: 4-EPEEDO-10, 2 mg/ml

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Naprod Life sciences Pvt. Ltd

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are appended as annex I

3. Scientific discussion

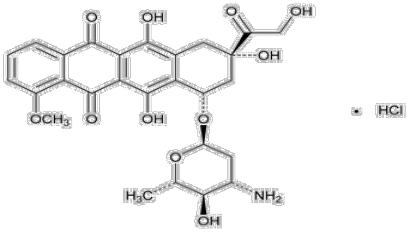
Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of DMF, Full details

General information
Epirubicin hydrochloride API is compendia in USP/BP
Molecular formula: $C_{27}H_{30}ClNO_{11}$

Chemical name: (8S,10S)-10-[(3-Amino-2,3,6-trideoxy-α-l-arabino-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

Structure:



Physico-chemical properties of the API

Epirubicin hydrochloride API is an arrange red powder that is soluble in water and in methanol, slightly soluble in anhydrous ethanol, practically insoluble in acetone. Epirubicin exhibit stereoisomerism due to the presence of 6 defines atom stereocenter count. No polymorphism has been reported for this molecule.

Manufacture

The API manufacturing site, INTAS Pharmaceuticals Limited(RPG Life Sciences Limited) 25, MIDC Land, Thane-Belapur Road, Navi Mumbai 400 705, India was noted to comply with GMP requirements as evidenced by the GMP certificate issued by Food & Drugs control Administration, Gandhinagar, Hujarat state, India . Epirubicin hydrochloride API is manufactured by fermentation synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per BP standards and ICHQ3A. The parameters monitored during quality control are: Appearance (Ph. Eur.,), solubility (Ph. Eur.,), identification (IR, HPLC), pH (Ph. Eur.,), water content (KF), acetone content (Ph. Eur.,), BET (Ph. Eur.,), related substances (HPLC), assay (HPLC), residual solvents (HS-GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Epirubicin hydrochloride API is 24 months when packed in double LDPE polyethylene bags and stored at 2ºC - 8ºC

Quality of the Finished Pharmaceutical Product

Formulation

4-EPEEDO-10 is an orange red colour lyophilized mass presented in a 5 ml 20mm flint tubular flint vial plugged with 20mm rubber stopper sealed and 20mm flip off aluminium seal 4-EPEEDO-10 contains Epirubicin hydrochloride and other ingredients listed here after: Lactose Monohydrate, Methyl paraben, Hydrochloric acid, Sodium Hydroxide and Water for Injection. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, Lactose and methylparaben are of safety concern therefore appropriate warnings should be included in the product label.

Manufacture

The finished product was manufactured at Naprod Life Sciences Pvt. Ltd., G-17/1, M.I.D.C. Tarapur industrial area, Boisar, dist – Thane – 401506, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 11th December, 2017

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: appearance (visual), identification (HPLC), uniformity of dosage unit (USP), constituted solution (USP), particulate matter (USP), pH (USP), bacterial endotoxins (USP), sterility (USP), water content (USP), related substance (HPLC), assay (HPLC) and content of methylparaben (HPLC). Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30 ± 2ºC, 75 ± 5% RH for 24 months and 40 ± 2ºC, 75 ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in type 1 glass vial with rubber stopper and aluminium seal pac at 30ºC

Safety and efficacy information

Safety and efficacy of 4-EPEEDO-10 was established through published literature as this is the generic medicines formulated as intravenous injection, therefore submission of clinical data was waived and this was supported by requirements prescribed on TMDA guidelines on Therapeutic equivalence requirements.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. 4-EPEEDO-10 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

NA

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label