THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR KEFROX (CEFUROXIME SODIUM EQUIVALENT TO CEFUROXIME 750MG) POWDER FOR SOLUTION FOR INJECTION OR INFUSION

Version number 1.0
21 August 2023

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1. Introduction

KEFROX injection is a generic medicinal version of “Zinacef 750 Injectie” by GlaxoSmithKlin contains Cefuroxime Sodium equivalent to Cefuroxime 750 mg per each vial. Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death. Cefuroxime is active against many Gram-positive and Gram-negative bacteria, including several beta-lactamase producing strains. KEFROX injection is approved in Tanzania for use in dults and children, including neonates (from birth).

1.1 Product details

Registration number	TAN 22 H 0256
Brand name	KEFROX injection
Generic name, strength, and form	Each sterile vial contains: Cefuroxime Sodium to Cefuroxime 750 mg
ATC classification	J01DC02- Cephalosporin antibiotic
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	CCL Pharmaceuticals (Pvt.) Ltd. 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan.
Local Technical Representative	HARLEY’s (T) Limited Plot No.3, Lot 20, Nyerere road P.O. Box 12589, Dar Es Salaam

1.2 Assessment procedure

The application for registration of KEFROX injection was submitted on 29/04 2021. The product underwent full assessment. Assessment was completed in 4(four) rounds of evaluation and the product was registered on 01 June 2023.

1.3 Information for users

Visual description of the finished product	A white fine, sterile powder, filled in 10ml labelled vial. Sealed with rubber stopper and blue color flip off seal packed in unit carton
Primary packing material	Glass (Type II) vials with rubber stoppers and blue color flip off seal packed
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C, store in a cool dry place, protect from light and moisture.
Route of administration	Intravenous and intramuscular injection
Therapeutic indications	Cefuroxime sodium is indicated for the treatment of the infections listed below in adults and children, including neonates (from birth).

	• Community acquired pneumonia • Acute exacerbations of chronic bronchitis • Complicated urinary tract infections, including pyelonephritis • Soft-tissue infections: cellulitis, erysipelas and wound infections • Intra-abdominal infections (see section 4.4) • Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section) In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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: KEFROX

Composition: Each sterile vial contains: Cefuroxime Sodium to Cefuroxime 750 mg

Pack size: 1 vial

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C, store in a cool dry place, protect from light and moisture

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: See enclosed leaflet

The details of the primary pack include:

Brand name and strength: KEFROX

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Wilshire Laboratories 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.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient

Information on the quality of the API was submitted in form of DMF.

Cefuroxime Sodium

General Information

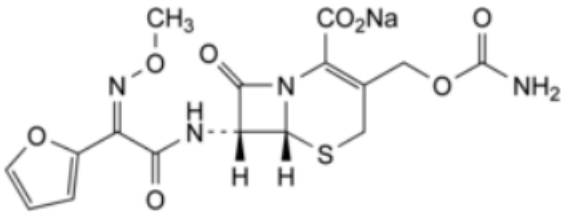
Cefuroxime Sodium API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{16}H_{15}N_4NaO_8S$

Chemical name:

Sodium(6R,7R)-7-[2-(2-furyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabi cyclo[4.2.0]oct-2- ene-2-carboxylate,7-(Z)-(O-methyloxime),carbamate

Structure:



General properties

The molecule has a molecular weight of 446.4 Da. It is white or almost white, slightly hygroscopic powder, freely soluble in water and very slightly). Four (4) asymmetric carbons are present in the

molecule. The substance shows stereoisomerism. Stereo chemical purity is controlled routinely by specific optical rotation (+59°~+66° in line with BP).

Cefuroxime sodium does not exhibit polymorphism. Nonetheless, this is not considered important as the active substance is present in solution in the finished product. The active is present in the drug product dissolved in water, hence the polymorphic form and particle size distribution are not considered as critical quality aspects.

Manufacture

Cefuroxime Sodium API manufacturer is Shenzhen Salubris Pharmaceuticals Co. Ltd, No. l, F enghuanggang Huabao Industrial District, Xixiang, Baoan District, Shenzhen, China 518102. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Shenzhen Food and Drug Administration. Cefuroxime Sodium is a semi-synthetic product derived from a fermentation product. 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: Description, solubility, appearance of solution, identification, specific optical rotation, related substances, pH, water, sterility, bacterial endotoxins, N,N-dimethyl aniline, 2-ethylhexanoic acid, residual solvents, foreign and particulate matter, assay (HPLC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Cefuroxime Sodium API is 60 months when packed in original container with storage condition ‘Preserve in well- closed containers. Store at room temperature’.

Quality of the Finished Pharmaceutical Product

Formulation

KEFROX is a white fine, sterile powder, filled in 10ml labelled vial. Sealed with rubber stopper and blue color flip off seal packed in unit carton.

KEFROX contains the Cefuroxime Sodium, with no another ingredient

Manufacture

The finished product manufacturers are Wilshire Laboratories Pvt. Ltd, 124/1 industrial Estate Kot Lakh pat, Lahore, Pakistan. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per BP and ICH requirements. The parameters monitored during quality control are: Physical appearance, identification by IR, water content, pH, colour after reconstitution, container closure integrity, bacterial endotoxin, sterility, particulate matters, related substances, uniformity of dosage units. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30 ± 2°C & RH: 65 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in glass (Type II) vials with rubber stoppers and blue color flip off seal packed with storage condition 'Do not store above 30°C, store in a cool dry place, protect from light and moisture.

Safety and efficacy information

KEFROX powder for solution for injection or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the part III: guidelines on therapeutic equivalence requirements, which states that a bioequivalence study is not required if the solutions for injection that contain the same active ingredients and excipients in the same concentrations as currently registered products and which are administered by the same route(s). The quantitative composition of KEFROX powder for solution for injection or infusion is entirely the same as the reference products in the market. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product

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. KEFROX solution for intravenous infusion 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

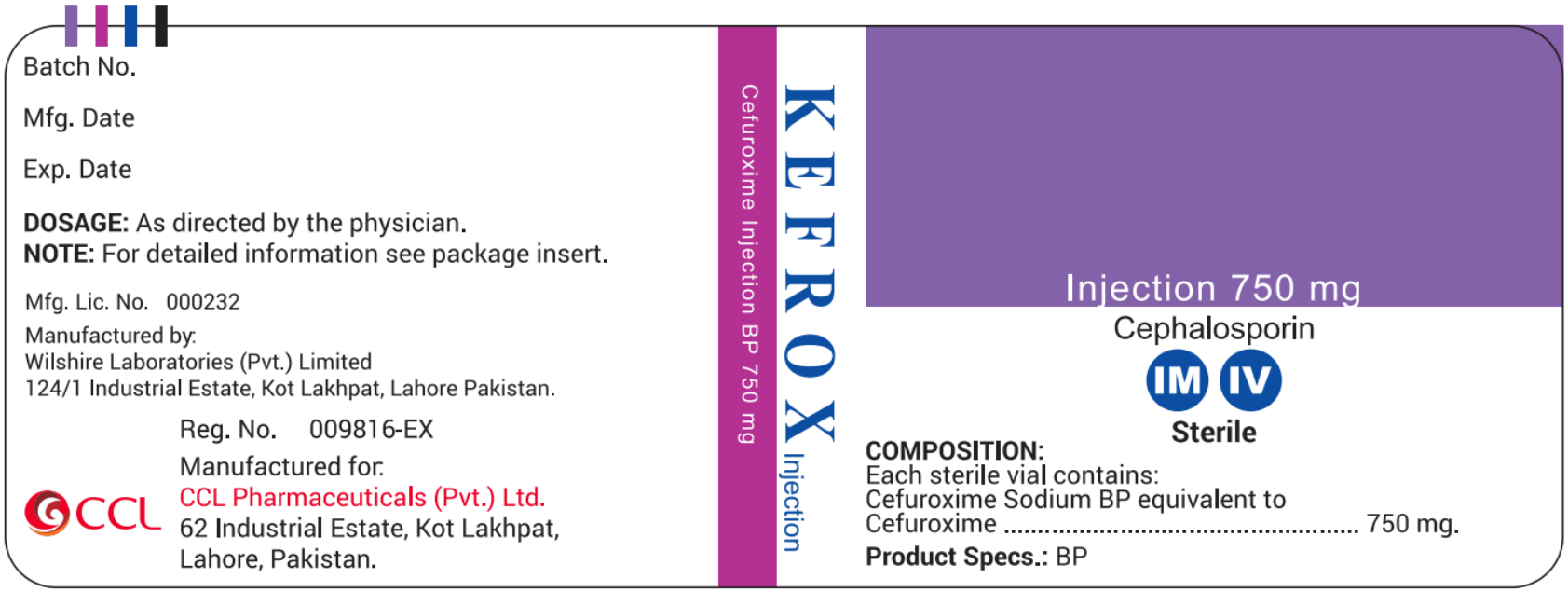
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

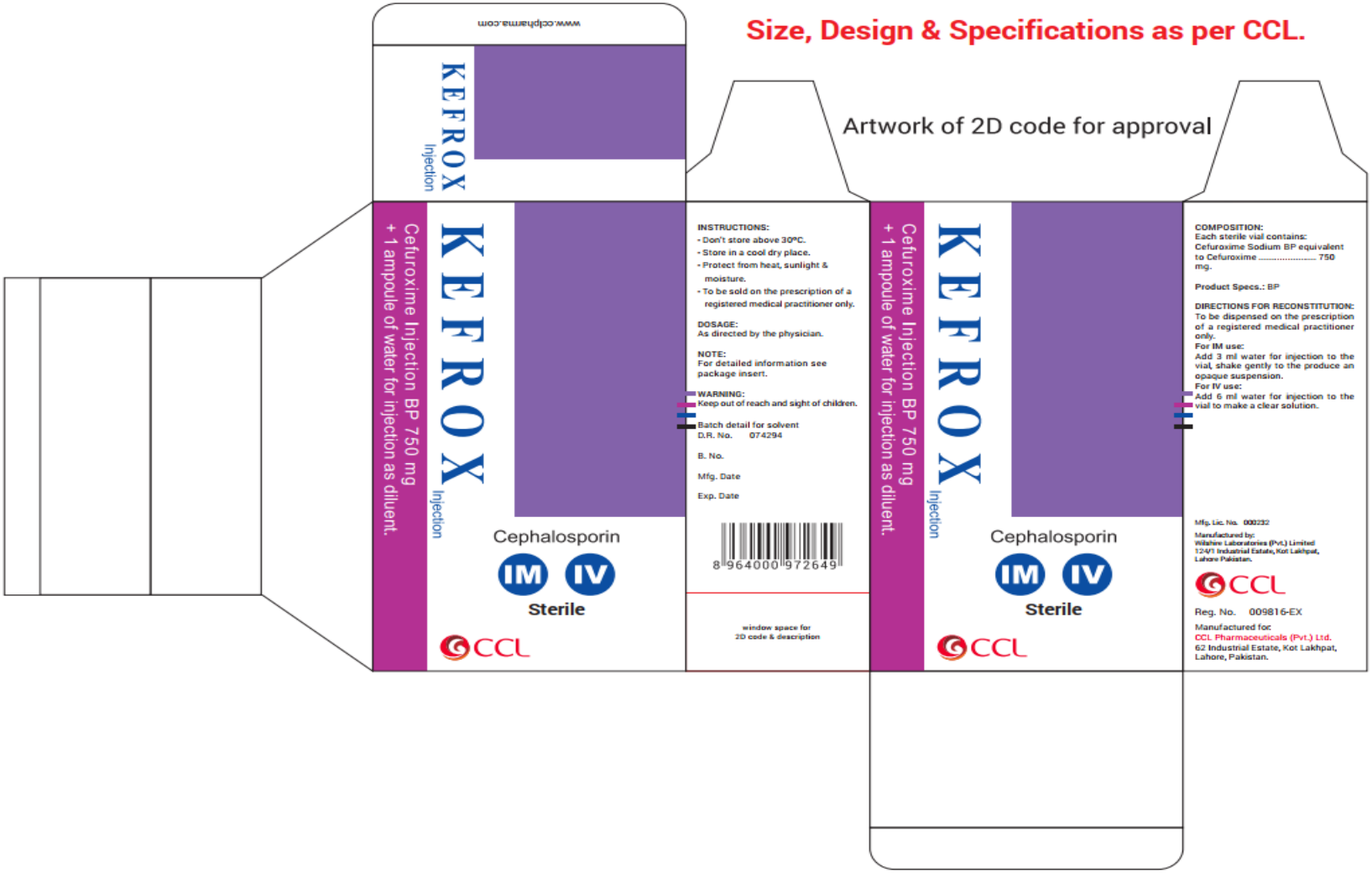
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;



Effective date: 03/10/2022