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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR THEOROXIME-250 DS (CEFUROXIME AXETIL USP) POWDER FOR ORAL SUSPENSION

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1. Introduction

Theoroxime-250 DS is a generic medicine of Cefuroxime 250 mg tablets. Theoroxime-250 DS is an antibiotic medicine belonging to J01DC02 second generation cephalosporin group. Theoroxime-250 DS exerts is activity by inhibiting 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. Theoroxime-250 DS is approved in Tanzania for use in paediatrics.

1.1 Product details

Registration number	TAN 20 HM 0198
Brand name	Theoroxime-250 DS
Generic name, strength and form	Cefuroxime axetil 250mg powder for oral suspension
ATC classification	J01DC02 second generation cephalosporin
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	Theon Pharmaceuticals Limited 400, Industrial Area, Phase-I, Panchkula- 134 J 13, Haryana India Telephone: +911725210200, 5011077, 5033850 Telefax: +91 172 5033851 E-Mail: cor12oratcoffice@theon12harma.com
Local Technical Representative	Heko Pharmacy

1.2 Assessment procedure

The application for registration of TAN 20 HM 0198 was submitted on 04/07/2017. The product underwent full assessment. Assessment was completed in 3 rounds of evaluation. Theoroxime-250 DS was registered on 25/07/2020.

1.3 Information for users

Visual description of the finished product	Yellow coloured granular powder gives yellow coloured suspension after reconstitution with water.
Primary packing material	60 mL HDPE bottle
Secondary packing materials	Carton box with 1 bottle
Shelf-life and storage condition	24 Months Store below 30ºC.Protect from light and moisture
Route of administration	Oral

Therapeutic indications	Cefuroxime is indicated for the treatment of the infections listed below in adults and children from the age of 3 months: •Acute streptococcal tonsillitis and pharyngitis. • Acute bacterial sinusitis. • Acute otitis media. • Acute exacerbations of chronic bronchitis. •Cystitis. •Pyelonephritis. •Uncomplicated skin and soft tissue infections. • Treatment of early Lyme disease.

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 simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:
Brand name: Theoroxime-250 DS
Composition: Cefuroxime axetil 250mg
Pack size: 60 ml
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store below 30ºC
Manufacturer address: Theon Pharmaceuticals Limited, Village Saini Majra,Tahsil Nalagarh, Dist-Solan, (H.P.)-174101 India

Unique identifier: NA
Special warnings/precautions or instructions for use: For paediatric use only.

The details of the primary pack include:
Brand name and strength: Theoroxime-250 DS
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Theon Pharmaceuticals Limited, Village Saini Majra,Tahsil Nalagarh, Dist-Solan, (H.P.)-174101 India
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.

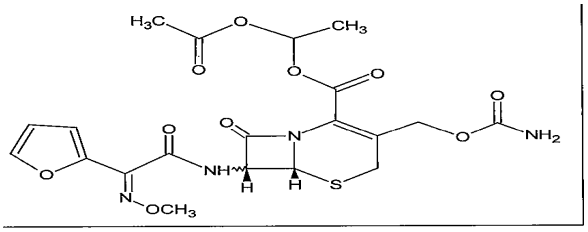
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Cefuroxime axetil API is compendia in USP.
Molecular formula: $C_{20}H_{22}N_4O_{10}S$
Chemical name: (6R,7R)-3-[[(Aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-Acetoxyethyl ester

Structure:



Critical physico-chemical properties of the API were slightly hygroscopic powder, freely soluble in acetone; soluble in chloroform, in ethyl acetate, and in methanol; slightly soluble in dehydrated alcohol; insoluble in ether and in water..

Manufacture
The API manufacturing site, Covalent laboratories Pvt limited. Address: Survey no.374, Gundla Machnoor Village, Hathnoor (Mandal), Medak (District)-502 296 Telangana, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Controlling Cum Licensing Authority, Baddi- Himachal Pradesh. Cefuroxime axetil API is manufactured by chemical 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 USP standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification, crystallinity, water,

diastereoisomers ration and assay.Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Losartan Potassium API is 48 months when packed in double polyethylene bags (inner transparent and outer black) twist-tied with plastic fastener and kept in HDPE container and stored at below 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Theoroxime-250 DS is a yellow coloured granular powder gives yellow coloured suspension after reconstitution with water.Theoroxime-250 DS contains cefuroxime axetil and other ingredients listed hereafter: neotame, flavour lemon special, quinoline yellow supra, mannitol, instacoat en-solution, isopropyl alcohol, dichloromethane, ethyl cellulose, sucrose, sodium benzoate, sodium citrate, flavour peppermint, anhydrous citric acid, colloidal anhydrous silica, xanthan gum.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, sucrose and sodium benzoate are of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Theon Pharmaceuticals Limited, village Saini Majra, Nalagarh, Dist-Solan, (H.P.)-174101India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 11-12/10/2016.

Specifications

The FPP is compendia in USP. The manufacturer controls the quality of the finished product as per USP standards and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, average fill weight, uniformity of filled weight, weight per ml, pH of reconstituted suspension, deliverable volume, water, dissolution, assay, microbiological limit test.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°C ± 2°C, 75 % ± 5 % for 24 months and 40°C ± 2°C, 75 % ± 5 % for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 60 ml HDPE bottle at below 30ºC.

Safety and efficacy information

Safety and efficacy of Theoroxime-250 DS was established through bioequivalence trial.
BE trial report number BRC/NR/10/010 was submitted.
In case of BE:

Study title	An open label, randomized, two treatment, two period, two sequence, single dose crossover comparative bioequivalence study of Cefuroxime axetil for oral Suspension USP containing Cefuroxime 250mg of Theon Pharmaceuticals Ltd, India with Zinnat® (cefuroxime axetil for oral suspension containing 125mg/5ml of 500 mg tablets) of GlaxoSmithKline, UK in normal healthy adult human male subject under fasting conditions.	
Study design	open label, randomized, two treatment, two period, two sequence, single dose crossover	
Study site	Bombay Bioresearch Center, plot no. 35, Ancillary Industrial Plots, Opp. Fire Brigade Colony, Govandi(East), Mumbai – 43, India.	
Study dates		
Primary objective	To compare the rate and extent of absorption of Cefuroxime axetil after administration Cefuroxime axetil for oral suspension USP containing Cefuroxime 250mg of Theon Pharmaceuticals Ltd, India with Zinnat® (Cefuroxime axetil) for oral suspension containing Cefuroxime 125mg/5ml of Glaxosmith kline, UK under fasting condition in healthy adult male subjects in a randomized cross over bioequivalence study.	
Secondary objective	To monitor the safety and tolerability of a single dose of Cefuroxime axetil for oral suspension USP 250mg when administered in 24 healthy human male subject under fasting condition.	
Number of participants	24	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞	
Investigational medicinal products	Test Product	Reference product
	Strength: 250 mg/5 ml Batch number: ECD10013 Expiry date: 12/2011	Strength: 125 mg/5ml Batch number: C585165 Expiry date: 08/2011
Analytical method	Liquid chromatography-tandem mass spectrometry	
Statistical method	ANOVA using GLM procedure SAS version 9.1.3	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)

AUC0-t (units)	10.099	10.509	95.944	88.954 – 103.484		15.350
AUC0-inf (units)	10.456	10.878	95.983	89.221 – 103.258		14.819
Cmax (units)	2.43	2.56	95.159	90.905 – 99.611		9.244

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Theoroxime-250 DS is equivalent and interchangeable with Zinnat® (cefuroxime axetil for oral suspension containing 125mg/5ml) suspension under acceptable in vivo experimental conditions.

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. Theoroxime-250 DS 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 label