TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR METHOREX (METHOTREXATE DISODIUM EQUIVALENT TO METHOTREXATE 2.5 MG) TABLETS

Version number 0.1

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1. Introduction

Methorex is a generic medicine of methotreaxate. Methotrex is an antioneoplastic medicine belonging to Immunosuppressive agent group. Methotres exerts is activity by inhibiting DNA synthesis, repair and cellular replication. Methotrexate is approved in Tanzania for use in adults, children and elderly .

1.1 Product details

Registration number	TAN 21 HM 0128
Brand name	Methorex 2.5
Generic name, strength and form	Methotrexate Disodium Equivalent to Methotrexate 2.5 mg
ATC classification	Pharmacotherapeutic group: Immunosuppressive agents ATC code: L04AX03
Distribution category	POM
Country of origin	India
Associated product	Nil
Marketing Authorization Holder	Cadila Healthcare Limited
Local Technical Representative	Abacus Pharna(A) Limited

1.2 Assessment procedure

The application for registration of Methotrex was submitted on 24.06.2019. The product underwent full assessment. Assessment was completed in three (3) rounds of evaluation. Methotrex was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	Yellow, round, uncoated tablets, with debossing “L2” on one side and scoring on other side.
Primary packing material	HDPE bottle pack of 100’s
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months “Store below 30°C” and “Store in the original container in order to protect from light”
Route of administration	Oral
Therapeutic indications	**Neoplastic Diseases** Indicated for treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate tablets, USP are used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types.

	Methotrexate tablets, USP are also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas. **Psoriasis** Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy. **Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis** Methotrexate is indicated in the management of selected adults with severe, active, rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

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 that is intended for long term use, 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: Methotrex 2.5
Composition: Methotrexate Tablets 2.5 mg, list of excipients: Microcrystalline cellulose 102, Lactose monohydrate, Anhydrous lactose, Magnesium stearate.
Pack size: HDPE bottle of 100's in a carton box
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store up to 30^0C, protect from light, keep out of reach of children
Manufacturer address: Cadila Healthcare Limited, Plot number 1-A/1&2, Pharmez (special economic zone), matoda, sarkhej Bavla, N.H.No.8A, Tal-sanad, Dist-Ahmedabad, India
Unique identifier: barcode
Special cautions: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician.

The details of the primary pack include:

Brand name and strength: Methotrex 2.5
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Cadila Healthcare Limited

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 up labels are appended as annex I.

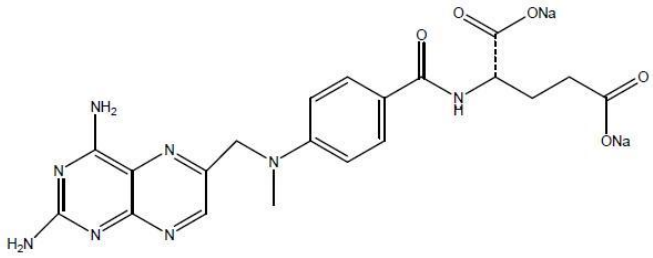
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Methotrexate disodium salt API is compendia in BP/Ph.Eur.
Molecular formula: C20H20N8O5Na2
Chemical name: L-Glutamic acid, N-[4-[[(2,4-diamino-6-teridinyl) methyl] methylamino] benzoyl]-, disodium salt Methotrexate disodium salt Sodium Methotrexate Glutamic acid, N-[p-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-, disodium salt, L-(+)-

Structure:



The API is soluble across the physiological pH range hence particle size and polymorphism are not considered as critical API parameters.

Manufacture
The API manufacturing site, Fernion Oy, Oulu Plant, Fermion Oy, P.O Box 28, FI-02101 Espoo, Finland was noted to comply with WHO GMP requirements. <Methotrexate> API is manufactured by <chemical> synthesis using <conventional/novel 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: description, identification, water content, heavy metals, related compounds, enantiomeric purity and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of methotrexate API is 60 months when packed in Aluminium laminated bag placed in a PE bag then fiber drum and stored at 25^0C.

Quality of the Finished Pharmaceutical Product

Formulation
Methotrex 2.5 is a yellow, round, uncoated tablets, with debossing 'L2' on one side and scoring on the other side packed in a HDPE bottle in a carton box. Methotrex 2.5 contains methotrexate disodium and other ingredients listed here after Microcrystalline cellulose 102, Lactose monohydrate, Anhydrous lactose, Magnesium stearate. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 17 in terms of function and quantities. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture
The finished product was manufactured at Cadila Healthcare Limited, Plot No 1A / 1 & 2 Pharmez Special Economic Zone, Sarkhej-Bavla N.H. No.8A, Near Village Matoda, Tal: Sanand, Dist: Ahmedabad, Gujarat: 382 213, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection.

Specifications
The FPP is compendia in BP and USP. The manufacturer controls the quality of the finished product as per BP and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, dissolution, average weight, uniformity of dosage units, assay, related substances, water content, microbial enumeration tests and hardness. 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 30ºC± 2ºC / 75% ±5% RH for 24 months and 40ºC ± 2ºC / 75% ±5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE bottle in a carton box at 30ºC.

Safety and efficacy information

Safety and efficacy of Methotrex 2.5 was established through bioequivalence trial.
BE trial report number CRL121318 was submitted.
In case of BE:

Study title	An open-Label, randomized, single-dose, two-period, two-treatment, two-sequence, crossover, multicentre, bioequivalence study of Methotrexate Tablets 2.5 mg of Cadila Healthcare Ltd., India and Methotrexate Tablets 2.5 mg of Dava Pharmaceuticals, USA in Adult Patients with Mild to Severe Psoriasis or Rheumatoid Arthritis Under Fasting Conditions.
Study design	An open-label, multicenter, single-dose, two-period, two-treatment, randomized, two-sequence, crossover study

	investigating the bioequivalence of Cadila Healthcare's Methotrexate tablets 2.5 mg to Dava Pharmaceuticals' Methotrexate tablets 2.5 mg following administration of a single oral dose of 2.5 mg in 32 patients	
Study site	1. Nirmal Hospital Private Ltd, Ring Road, Civil street, Near Kadiwala school, Surat 395002, Gujarat. 2. Rathi Hospital, Nr. Anupam Shopping Centre, Opp. Mahabaleshwar Society, Jodhpur cross road, Satellite, Ahmedabad-380015, Gujarat. 3. Malpani Multispecialty Hospital, SP-6, Road No. 1, VKI Area, Sikar Road, Jaipur-302013, Rajasthan. 4. Grant Medical Foundation, Ruby Hall Clinic, 40, Sassoon Road, Pune-411001, Maharashtra. 5. Sapthagiri Institute of Medical Sciences and Research Center, #15, Chikkasandra, Hesaraghatta Main Road, Bangalore-560090, Karnataka. 6. Centre for Rheumatic Disease, 11 Hermes Elegance, 1988 Convent Street, Camp, Pune-411 001, Maharashtra.	
Study dates	13 April 2014 - 18 May 2014	
Primary objective	To evaluate the pharmacokinetic bioequivalence of oral Methotrexate Tablets 2.5 mg of Cadila Healthcare Ltd., India with Methotrexate Tablets 2.5 mg of DAVA Pharmaceuticals, USA in patients with Mild to Severe Psoriasis or Rheumatoid Arthritis under fasting conditions and to monitor safety of the patients.	
Secondary objective		
Number of participants	31	
Monitored parameters		
Investigational medicinal products	Test Product	Reference product
	Strength: 2.5 mg Batch number: EOD001 Expiry date:	Strength: 2.5 mg Batch number: 1310616A Expiry date: Sep 2016
Analytical method	LC/MS/MS	
Statistical method	ANOVA	

Efficacy results are summarized as follows:

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**	**CV (%)**
AUC0-t (units)						
AUC0-inf (units)	292.671	290.960	100.59%	95.54%;105.91%)	29	11.977
Cmax (units)	84.402	85.588	98.61%	92.96%;104.61%	29	13.746

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, methotrex 2.5 is equivalent and interchangeable with methotrexate tablet 2.5 mg manufactured by DAVA Pharmaceuticals, USA 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. methotrex 2.5 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