THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR UNIPROEX ER 500 (DIVALPROEX SODIUM 500 MG) EXTENDED-RELEASE TABLETS

Version number 01,

06/01/2023

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1. Introduction

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Uniproex ER 500 is approved in Tanzania for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

1.1 Product details

Registration number	TAN 22 HM 0509
Brand name	Uniproex ER 500 Extended-Release tablets
Generic name, strength and form	Divalproex Sodium equivalent to Valproic acid
ATC classification	Psycholeptics, Antipsychotics, Other Antipsychotics, ATC Code: N05AX
Distribution category	POM
Country of origin	India
Associated product	The finished product is presented as a film-coated tablet containing 250 mg of Divalproex Sodium as active substance
Marketing Authorization Holder	Unichem Laboratories Ltd, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (west), Mumbai – 400 102 India
Local Technical Representative	Astra Pharma (T) Ltd. Plot no-12, Vingunguti Industrial Area, Nyerere Road, Opp: Pepsi Tanzania Dar es Salaam

1.2 Assessment procedure

The application for registration of Uniproex ER 500 Extended-Release tablets was submitted on 14/03/2022. The product underwent abridged assessment. Assessment was completed in two rounds of evaluation. Uniproex ER 500 Extended-Release tablets was registered on 05/12/2022.

1.3 Information for users

Visual description of the finished product	Yellow colored, oval shaped, biconvex film coated tablets imprinted with “U 381” on one side and plain on the other
Primary packing material	Pack of 3 x 10’s tablets in Alu-Alu and Aclar-PVC pack
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	24 months Store below 30°C, protect from light and moisture
Route of administration	Oral
Therapeutic indications	Uniproex ER 500 Extended-Release tablets are indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features

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 both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Uniproex ER 500 Extended-Release tablets
Composition: Each Extended-Release tablets 500 mg of Valproic acid
Pack size: 3 x 10’s tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store below 30°C, protect from light and moisture
Manufacturer address: Unichem Laboratories Limited, Plot Nos. 15-18, Pilerne Industrial Estate, Pilerne, Bardez – Goa – 403511, India

Unique identifier: N/A
Special warnings/precautions or instructions for use: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The details of the primary pack include:
Brand name and strength: Uniproex ER 500 Extended-Release tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Unichem Laboratories Limited, Plot Nos. 15-18, Pilerne Industrial Estate, Pilerne, Bardez – Goa – 403511, 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.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

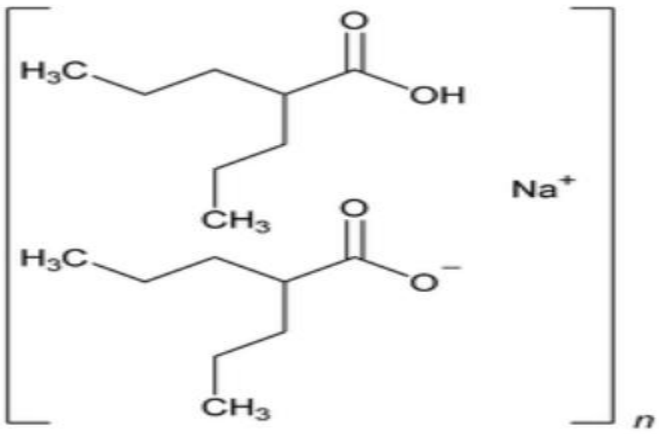
Information on quality of the API was submitted in form of full details.

General properties
Divalproex Sodium API is compendia in USP Pharmacopeia

Molecular formula: $(C_{16}H_{31}NaO_4)_n$

Chemical names:
Pentanoic acid, 2-propyl – sodium salt (2:1); Sodium hydrogen bis (2- propylvalerate)

Structure:



Critical physico-chemical properties are:

The active substance is white to off white powder. It is freely soluble in methanol, soluble in acetone, practically insoluble in acetonitrile

Manufacture

The API manufacturing site; Anjan Drug Private Limited, Plot Nos.: 109, 110, 115 & 116, SIDCO Pharmaceutical Industrial Estate, Old Mamallapuram Road, Alathur – 603 110, Kanchipuram District, Tamilnadu, India. The manufacturing facilities were noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Office of the Director of Drugs Controls Tamil Nadu Chennar, India. Divalproex Sodium 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: Appearance, solubility, Identification (IR, HPLC), chemical test for Sodium, Water (by KF) USP<921>, Assay (HPLC) and related substances (HPLC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The stability results indicate that the active substance made by the proposed manufacturers is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container which has been demonstrated.

Quality of the Finished Pharmaceutical Product

Formulation

Uniproex ER 500 Extended-Release tablets is presented as yellow coloured, oval shaped, biconvex film coated tablets imprinted with "U 381" on one side and plain on the other.

Uniproex ER 500 Extended-Release tablets contains Lactose Monohydrate, Ethylcellulose, Hypromellose, Colloidal Silicon Dioxide, Talc, Stearic Acid, Opadry II 32K520229 Yellow, Opacode Black S-1-277001, Isopropyl Alcohol and Purified water. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Film coat:

Opadry II 32K520229 Yellow contains: Hypromellose, Lactose Monohydrate, Titanium Dioxide, Triacetin and Yellow Iron Oxide.

Imprinting Ink - Opacode S-1-277001 contains: Shellac Glaze, Ferrosoferric Oxide, N-Butyl Alcohol, Purified Water, Propylene Glycol, Dehydrated Ethanol and Isopropyl Alcohol.

Manufacture

The finished product was manufactured at Unichem Laboratories Limited, Plot Nos. 15-18, Pilerne Industrial Estate, Pilerne, Bardez – Goa – 403511, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 08/01/2020

Specifications

The FPP is compendia in USP. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: appearance, identity (HPLC and UV spectrum), water determination (by KF) USP <921> Uniformity of dosage units by weight variation USP <905>, Dissolution (USP <711>) (By HPLC) (In House), degradation products (HPLC), assay (HPLC), microbial purity and Residual solvent. 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 & 75% ± 5% RH for 24 months and 40 ± 2°C & 75% ± 5% RH for 6 months. Based on available stability data, the proposed shelf-life of 24 months is acceptable.

Safety and efficacy information

Safety and efficacy information

Safety and efficacy of UniproeX ER 500 was established through bioequivalence trial BE trial report number 085-18 version 0.0 was submitted.

Study title	A randomized, open label balanced, two treatments, four period, two sequence, single dose, crossover, fully replicated, bioequivalence study of Divalproex Sodium Extended-Release Tablet 500 mg of Unichem Laboratories Ltd., India with Depakote ER (Divalproex Sodium) Extended-Release Tablets 500 mg, Manufactured by Abbvie Inc., North Chicago, IL 60064 U.S.A. Or Abbvie Ltd, Barceloneta, PR 00617 for Abbvie Inc., North Chicago, IL 60064 U.S.A in healthy human adult male and/or female subjects under fasting conditions.
Study design	A randomized, open label balanced, two treatments, four period, two sequence, single dose, crossover, fully replicated
Study site	Ecron Acunova Limited (Formerly known as Manipal Acunova Limited), V floor, MCODS Building, KMC Hospital, Attavar, Mangalore- 575 001, India
Study dates	Critical Study dates Period I: 26 April 2019– 01 May 2019 Period II: 06 May 2019 - 11 May 2019 Period III: 15 May 2019 - 20 May 2019 Period II: 23 May 2019 - 28 May 2019 Bioanalytical: 01 Jun 2019 – 16 Jun 2019
Primary objective	To assess the single-dose oral bioequivalence of Valproic Acid from Divalproex Sodium Extended-Release Tablet 500 mg of Unichem Laboratories Ltd., India with Depakote ER (Divalproex Sodium) Extended-Release Tablets 500 mg, manufactured by Abbvie Inc., North Chicago, IL 60064 U.S.A. Or Abbvie Ltd, Barceloneta, PR 00617 for Abbvie Inc., North Chicago, IL 60064 U.S.A in healthy human adult male and/or female subjects under fasting conditions
Secondary objective	To monitor the safety and tolerability of a single dose of Divalproex Sodium Extended-Release Tablet 500 mg when administered in healthy human adult male and/or female subjects under fasting conditions
Number of participants	52
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation

	Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 500 mg Batch number: GDVH19003 Expiry date: Jan 2021	Strength: 500 mg Batch number: 1067329 Expiry date: June 2019
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	----------	

Efficacy results are summarized as follows:

Parameter	Geometric Least Square Mean (GLSM)				Ratio	90% CI
	N	Test Product (A)	N	Reference Product (B)		
Cmax (µg/mL)	96	28.409	97	26.778	106.09	(98.68, 114.06)
AUC0-t (µg.hr/mL)	94	906.804	95	900.324	100.72	(91.67, 110.66)
AUC0-∞ (µg.hr/mL)	94	1007.575	95	1002.129	100.54	(92.01, 109.87)

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, UniproeX ER 500 is equivalent and interchangeable with Depakote ER (Divalproex Sodium Extended-Release Tablets) 500 mg under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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 UniproeX ER 500 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