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MINISTRY OF HEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR DICORATE ER 500 (DIVALPROEX SODIUM 500MG) EXTENDED-RELEASE TABLET

Version number 01

3rd January, 2023

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1. Introduction

Dicorate ER 500 is a generic medicine of Depakote. Dicorate ER 500 is a Antiepileptics medicine belonging to N05AX Psycholeptics, Antipsychotics, Other Antipsychotic group. Dicorate ER 500 exerts is activity by potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA. Dicorate ER 500 is approved in Tanzania for use in adults, elderly.

1.1 Product details

Registration number	TAN 21 HM 0190
Brand name	Dicorate ER 500
Generic name, strength and form	Divalproex sodium Equivalent To Valproic Acid 500 mg
ATC classification	N05AX Psycholeptics, Antipsychotics, Other Antipsychotic
Distribution category	POM
Country of origin	India
Associated product	Dicorate ER 250
Marketing Authorization Holder	Sun Pharmaceutical Industries ltd, Sun House, Plot No. 201 B/1, Western Express Highway, Goregoan (E), Mumbai, Maharashtra **India**
Local Technical Representative	Salama Pharmaceuticals Limited P.O. Box 65235, Dar es Salaam

1.2 Assessment procedure

The application for registration of Dicorate ER 500 was submitted on 24th March, 2020. The product underwent full assessment. Assessment was completed in two rounds of evaluation. Dicorate ER 500 was registered on 29th march, 2021.

1.3 Information for users

Visual description of the finished product	Grey color, oval, biconvex, coated tablet plain on both sides

Primary packing material	Aluminium printed foil blisters
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months Store below 30 ºC in dry place
Route of administration	Oral
Therapeutic indications	Treatment of manic episodes associated with bipolar disorder (manic-depressive illness), a condition with symptoms of excitement or euphoria

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: Dicorate ER 500

Composition: Divalproex sodium equivalent to Valproic acid 500 mg, hydrogenated castor oil, anhydrous Lactose, Hypromellose, Isopropyl alcohol, purified water, Talc, Magnesium stearate, Silicon dioxide, Opadry 03F57509 grey

Pack size: 10’s in a blister, 5 blisters in a carton box

Manufacturing details: <batch number, manufacturing date, expiry date>

Storage conditions: Store below 30 ºC in dry place

Manufacturer address: Sun Pharmaceutical Industries Ltd, Survey No. 214, Plot No. 20, G.I.A. Phase-II, Piparia, Silvassa- 396 320, U.T. of Dadra & Nagar Haveli, India

Unique identifier: NA

Special warnings/precautions or instructions for use: <include warnings or IFU if applicable

The details of the primary pack include:

Brand name and strength: Dicorate ER 500 (Divalproex sodium equivalent to Valproic acid 500 mg)
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: Sun Pharmaceutical Industries 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.

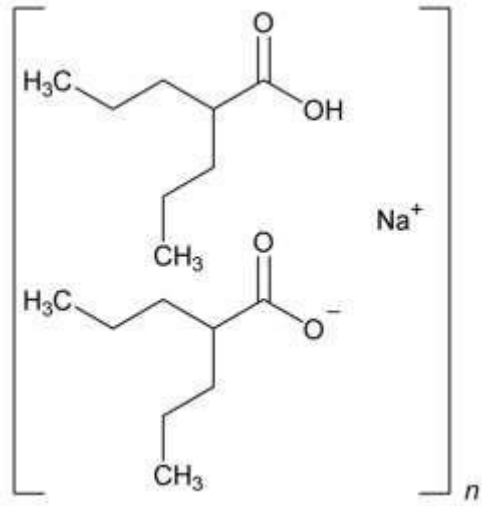
Mock labels are appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Divalproex sodium API is compendia in USP/BP.
Molecular formula: $C_{16}H_{31}NaO_4)n$
Chemical name: Sodium hydrogen bis(2-propylvalerate) oligomer or Pentanoic acid, 2-propyl-, sodium salt
Structure:



Sodium valproate is crystalline powder which is hygroscopic and very soluble in water while Valproic acid is a colorless or very slightly yellow, clear liquid, which is slightly viscous and Very slightly soluble in water.

Manufacture

The API manufacturing site, Sun Pharmaceutical Industries Limited A-7/A-8, M.I.D.C., Industrial Area, Ahmednagar – 414 111, Maharashtra, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>. 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, in-house standards and ICHQ3A. The parameters monitored during quality control are: appearance, solubility, identification, assay, water content, chloride content, sulphated ash, residual solvents, related substances. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Divalproex sodium API is 60 months when packed in low density polyethylene bags (inner transparent and outer black bag) placed in fiber board drum under nitrogen atmosphere and stored at 25°C/60% RH.

Quality of the Finished Pharmaceutical Product

Formulation

Dicorate ER 500 is a grey colour, oval, biconvex coated tablet plain on both side packed in Aluminium printed foil blister. Describe the diluent, measuring devices or any delivery device if applicable. Dicorate ER 500 contains Divalproex sodium and other ingredients listed here after hydrogenated castor oil, anhydrous Lactose, Hypromellose, Isopropyl alcohol, purified water, Talc, Magnesium stearate, Silicon dioxide, Opadry 03F57509 grey. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition <number> in terms of function and quantities. Ingredient, anhydrous Lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Sun Pharmaceuticals Industries Ltd., Survey No.214, Plot No. 20, G.I.A., Phase II, Piparia, Silvassa – 396230, U.T. of Dadra & Nagar Haveli, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 2017.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: Description, Identification (by HPLC), Average Weight, Dissolution (By HPLC), Uniformity of Dosage Units (By weight variation), Assay (By HPLC), Related Substances (By GC) and Microbial 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 three batches of the finished product stored at 30ºC ± 2ºC/ 60% ± 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 Aluminium printed foil blisters at store below 30ºC in dry place.

Safety and efficacy information

Safety and efficacy of Dicorate ER 500 was established through bioequivalence trial. BE trial report number PKD_14_373 was submitted.

In case of BE:

Study title	a randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of divalproex sodium 500 mg extended release tablets manufactured by sun pharmaceutical industries limited, india and depakote® er (divalproex sodium) 500 mg extended release tablets manufactured by abbott laboratorios do brasil ltda, in 40 healthy human adult subjects under fed conditions.
Study design	randomized, open label, two treatment, two periods, two sequences, single dose, and crossover bioequivalence study with 10 days washout between each dosing, conducted under fed condition.
Study site	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 India

<table>
<tr><td>Study dates</td><td colspan="2"><table><tr><th>Activities</th><th>Dates</th></tr><tr><td>Period I (dosing)</td><td>07/04/2015</td></tr><tr><td>Period II (dosing)</td><td>17/04/2015</td></tr><tr><td>Analysis (start date)</td><td>14/04/2015</td></tr><tr><td>Analysis (completion date)</td><td>22/04/2015</td></tr></table></td></tr>
<tr><td>Primary objective</td><td colspan="2">To compare the bioequivalence and characterize the pharmacokinetic profile of the sponsor’s divalproex sodium 500 mg extended release tablets manufactured by sun pharmaceutical industries limited, india relative to that of reference product “depakote® er (divalproex sodium) 500 mg extended release tablets” manufactured by abbott laboratorios do brasil ltda in healthy, adult, human male subjects under fedconditions and to assess the bioequivalence</td></tr>
<tr><td>Secondary objective</td><td colspan="2">To monitor the safety of the subjects</td></tr>
<tr><td>Number of participants</td><td colspan="2">40 healthy male</td></tr>
<tr><td>Monitored parameters</td><td colspan="2">AUC, Cmax, Tmax, T1/2, Kel</td></tr>
<tr><td rowspan="2">Investigational medicinal products</td><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 500 mg
Batch number: SKM0986
Expiry date: 05/2015</td><td>Strength: 500 mg
Batch number: 39330QA
Expiry date: 11/2015</td></tr>
<tr><td>Analytical method</td><td colspan="2">UHPLC/MS/MS</td></tr>
<tr><td>Statistical method</td><td colspan="2">SAS (release 9.2 for Windows</td></tr>
</table>

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.h/mL)	1378.32	1254.41	109.88	104.44 – 115.60	38	13.16
AUC0-inf (units)						
Cmax (ng/mL)	39.89	36.15	110.33	104.80 – 116.15	38	13.34

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, Dicorate ER 500 is equivalent and interchangeable with < depakote® er (divalproex sodium) 500 mg extended release tablets 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. Dicorate 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