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MINISTRYOFHEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TORLEVA 750 (LEVETIRACETAM 750MG), TORLEVA 500(LEVETIRACETAM 500MG) AND TORLEVA 250 (LEVETIRACETAM 250MG) TABLETS

Version number 1.0
12 October 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253,
Dodoma - Tanzania,
Tel: +255 (26) 2961989/2061990/ +255(22) 2450512/2450751/2452108,
Email: info@tmda.go.tz, Website: www.tmda.go.tz,
Toll free: 08001100834

1. Introduction

Torleva is a generic medicine of Levetiracetam Tablets. Torleva is a an antiepileptic, medicine belonging to N03AX14- other antiepileptics group. Torleva exerts is activity by multiple mechanisms including the effect on intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. It also partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Torleva is approved in Tanzania for use in adults and children.

1.1 Product details

Registration number	Torleva 750: TAN 20 HM 0396 Torleva 500: TAN 20 HM 0390 Torleva 250: TAN 20 HM 0349
Brand name	Torleva 750 Torleva 500 Torleva 250
Generic name, strength and form	Levetiracetam Tablets 750mg Levetiracetam Tablets 500mg Levetiracetam Tablets 250mg
ATC classification	N03AX14- other antiepileptics
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	Torrent Pharmaceuticals Limited (TPL) Torrent House, Off. Ashram Road Ahmedabad-380 009 Gujarat, India
Local Technical Representative	Phillips Distributors Limited, Plot No.:111, Vingunguti Industrial area P.O. Box No. 737, Dar-es-Salam, Tanzania

1.2 Assessment procedure

The application for registration of Torleva was submitted on 09/10/2013. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Torleva was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Torleva 750: Orange coloured, oval shaped, film coated tablets debossed with breakline separating '750' and 'MG' on one side and '1016' on other side

	Torleva 500: Yellow coloured, oval shaped, film coated tablets debossed with breakline separating '500' and 'MG' on one side and '1015' on other side Torleva 250: Blue coloured, oval shaped, film coated tablets debossed with breakline separating '250' and 'MG' on one side and '1014' on other side.
Primary packing material	Aluminium-PVC/PVDC Blister
Secondary packing materials	
Shelf-life and storage condition	48 months Store below 30°C protected from moisture
Route of administration	Oral
Therapeutic indications	As adjunctive therapy in treatment of partial onset seizures in adults with epilepsy. (i) As monotherapy in partial onset seizures with or without secondary generalisation in patients with 16 years of age with newly diagnosed epilepsy. (ii) As adjunctive therapy in myoclonic seizures in adults and adolescents from 12 years of age with Juvenile myoclonic epilepsy. (iii) In primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

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: Torleva 750

Composition: Levetiracetam tablets

Pack size: 3 × 10 tablets

Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store below 30°C protected from moisture
Manufacturer address: Torrent Pharmaceuticals Limited (TPL) ,Ahmedabad-Mehsana Highway , Taluka – Kadi, District: Mehsana ,Indrad – 382 721 ,Gujarat, India
Unique identifier: <state the unique identification used>
Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:
Brand name and strength:
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: Torrent Pharmaceuticals 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.
Describe any approved deviation to the requirements and the justification for the deviation.

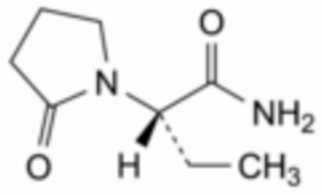
Mock labels are appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Levetiracetam (Form-I) API is compendia in USP/BP.
Molecular formula: $C_8H_{14}N_2O_2$
Chemical name: (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide
Structure:



Critical physico-chemical properties of the API were very soluble in water and exhibits polymorphism whereas form-I is manufactured.

Manufacture

The API manufacturing site, Hetero labs limited, S. No. 10, I.D.A, Gaddapotharam, Jinnaram Mandal, Medak District,, Andhra Pradesh, INDIA was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>.
The API manufacturing site, Dr. Reddy's Laboratories Limited, Chemical Technical Operations, Unit-VI, APIIC Industrial Estate Pydibhimavaram, Ranasthalam Mandal, Srikakulam District-532409, Andhra Pradesh, India
was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>. Levetiracetam 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 Ph.Eur standards and ICHQ3A. The parameters monitored during quality control are: description, solubility,Identification, water content, appearance of solution, sulphated ash, heavy metals,enantiometric purity, Related substances, assay, 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 Levetiracetam API is 60 months when packed in transparent polyethylene bag and stored at 25^0C.

Quality of the Finished Pharmaceutical Product

Formulation

Torleva 750 is an orange coloured, oval shaped, film coated tablets debossed with breakline separating '750' and 'MG' on one side and '1016' on other side.
Torleva 500 is a yellow coloured, oval shaped, film coated tablets debossed with breakline separating '500' and 'MG' on one side and '1015' on other side.
Torleva 250 is a blue coloured, oval shaped, film coated tablets debossed with breakline separating '250' and 'MG' on one side and '1014' on other side.
Torleva contains Levetiracetam and other ingredients listed hereafter maize starch, sodium starch glycolate, colloidal silicon dioxide, povidone K 30, talc, magnesium stearate, hypromellose, titanium dioxide, macrogols 400 (polyethylene glycol 400), feric oxide red, lake of sunset yellow, ferric oxide yellow, lake of indigo carmine.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, <excipient> is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Torrent Pharmaceuticals Limited (TPL) ,Ahmedabad-Mehsana Highway , Taluka – Kadi, District: Mehsana ,Indrad – 382 721 ,Gujarat, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 2019.

Specifications

The FPP is <non-compendia/compendia in BP/USP/JP/International Ph>. The manufacturer controls the quality of the finished product as per <reference monograph(BP/USP/JP/International Ph/in-house)> and ICHQ3B requirements. The parameters monitored during quality control are: description, Identification, identification of colorants, average weight, water content, uniformity of dosage units, dissolution, related substances and assay. 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 30ºC±2ºC/75%±5%RH for 48 months and 40°C ± 2°C/75 ± 5 % RH for 6 months. Based on the stability data presented, the approved shelf-life is 48 months when stored in Alu-PVC/PVdC blisters at below 30°C.

Safety and efficacy information

Torleva 750

Safety and efficacy of Torleva 750 was established through biowaiver application. Comparative dissolution report number <number> was submitted.
The biowaiver was approved based on additional strength.

Torleva 750 tablets fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Torleva 750 tablets was compared to Torleva (Levetiracetam) 1000 tablets.At least 85% of the labelled amount of Levetiracetam had dissolved in all three media. Therefore, confirming similarity.

Torleva 500

Safety and efficacy of Torleva 500 was established through biowaiver application. Comparative dissolution report number <number> was submitted.

The biowaiver was approved based on additional strength.

Torleva 500 tablets fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Torleva 500 tablets was compared to Torleva (Levetiracetam) 1000 tablets.At least 85% of the labelled amount of Levetiracetam had dissolved in all three media. Therefore, confirming similarity.

Torleva 250

Safety and efficacy of Torleva 250 was established through biowaiver application. Comparative dissolution report number <number> was submitted.

The biowaiver was approved based on additional strength.

Torleva 250 tablets fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Torleva 250 tablets was compared to Torleva (Levetiracetam) 1000 tablets.At least 85% of the labelled amount of Levetiracetam had dissolved in all three media. Therefore, confirming similarity.

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. Torleva 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

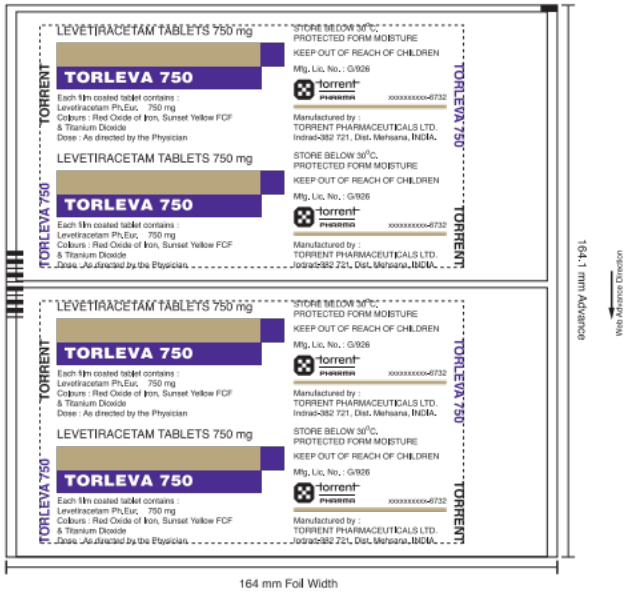
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

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

Annex I: Mock up label

Torleva 750



Torleva 500
Torleva 250