THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GULEVON (LEVETIRACETAM 500MG) FILM COATED TABLETS

Version number 1.0
21 August, 2023

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1. Introduction

Gulevon tablets is a generic medicinal product containing the active substance levetiracetam. The reference medicinal product is Keppra 500 mg film-coated tablets from UCB Pharma. The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. Gulevon tablets is approved in Tanzania for use in adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more.

Product details

Registration number	TAN 23 HM 0257
Brand name	Gulevon
Generic name, strength, and form	Each film-coated tablet contains 500 mg Levetiracetam
ATC classification	N03AX14, antiepileptics, other antiepileptics
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	B&O PHARM ZAC de la Masquère - 500 rue de l'Hers – 31750 Escalquens, France
Local Technical Representative	Tridem Pharma Tanzania Limited P.O Box 23145, Dar es Salaam

1.1 Assessment procedure

The application for registration of Gulevon was submitted on DD/MM/YYY. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Biconvex and oval tablets, scored and debossed with the code "J" and "X" on one side. Other side is smooth. It is white or off-white after removal of the coating. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses
Primary packing material	PVC blister and Al foil
Secondary packing materials	Printed carton box
Shelf-life and storage condition	36 months, Do not store above 30 ^{o}C

Route of administration	Oral
Therapeutic indications	Indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Indicated as adjunctive therapy • in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy. • in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. • in the treatment of 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: Gulevon

Composition: Each film-coated tablet contains 500 mg Levetiracetam

Pack size: 60 tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not above 30°C

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Not applicable

The details of the primary pack include:

Brand name and strength: Gulevon

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: B&O PHARM

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 Ingredients

Information on quality of the API was submitted in form of CEP.

General Information

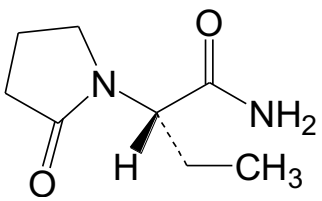
Levetiracetam API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{14}N_2O_2$

Chemical name:

(2S)-2-(2-Oxopyrrolidin-1-yl)butanamide

Structure:



General properties

Levetiracetam is a white to off-white crystalline powder very soluble in water. It is also freely soluble in chloroform and in methanol, soluble in ethanol, sparingly soluble in acetonitrile, and insoluble in n-hexane. It is slightly hygroscopic and presents one single asymmetric centre, leading to 2 optical isomers, where the active is the S-enantiomer. According to the synthetic process described in this application the active substance is consistently obtained as the S-enantiomer and is routinely controlled with an enantiomeric purity test. Levetiracetam does not present polymorphism. The same polymorphic form is obtained (demonstrated by XRD)

Manufacture

Levetiracetam API manufacturer is Shangyu Jingxin Pharmaceutical Co.,Ltd. No 31, Weisan Road,Zhejiang Hangzhou Bay, Shangyu Industrial area, Shangyu city,Zhejiang Province, P.R.China, 3122369, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the China Food and Drug Administration. 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, identity by IR and HPLC, enantiomeric purity, appearance of solution, enantiomeric purity (impurity D), impurity G, related substances, heavy metals, water, sulfated ash, assay (HPLC), residual solvent (GC). 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 24 months when packed in original container with storage condition “Store at temperature below 25 °C.”.

Quality of the Finished Pharmaceutical Product

Formulation

Gulevon is a biconvex and oval tablet, scored and debossed with the code “J” and “X” on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. other side is smooth. It is white or off-white after removal of the coating.

Gulevon contains the Levetiracetam and other ingredients listed here after: pregelatine starch, microcrystalline cellulose 102, croscarmellose sodium, polyethylene glycol 4000, hypromellose, silicon dioxide, magnesium stearate, purified water, film coating premixed agent (gastric soluble type): partially hydrolyzed polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, soy lecithin, iron oxide red, iron oxide yellow. The quantities of all ingredients are confirmed to be in

line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Zhejiang Jingxin Pharmaceutical Co., Ltd, No.800 Xinchang East Road, Yulin Subdistrict, Xinchang County, Zhejiang, China. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is compendia in USP. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: description, identification, impurities, assay, dissolution, microbiological contamination. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 36 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in PVC blister and Al foil with storage condition 'Do not above 30°C'

Safety and efficacy information

The biowaiver was approved based on additional strength.

Gulevon fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Gulevon (Levetiracetam 500mg) Film Coated Tablets was compared to Gulevon (Levetiracetam 1000mg) Film Coated Tablets. Less than 85% of the labelled amount of Levetiracetam had dissolved in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

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. Gulevon 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

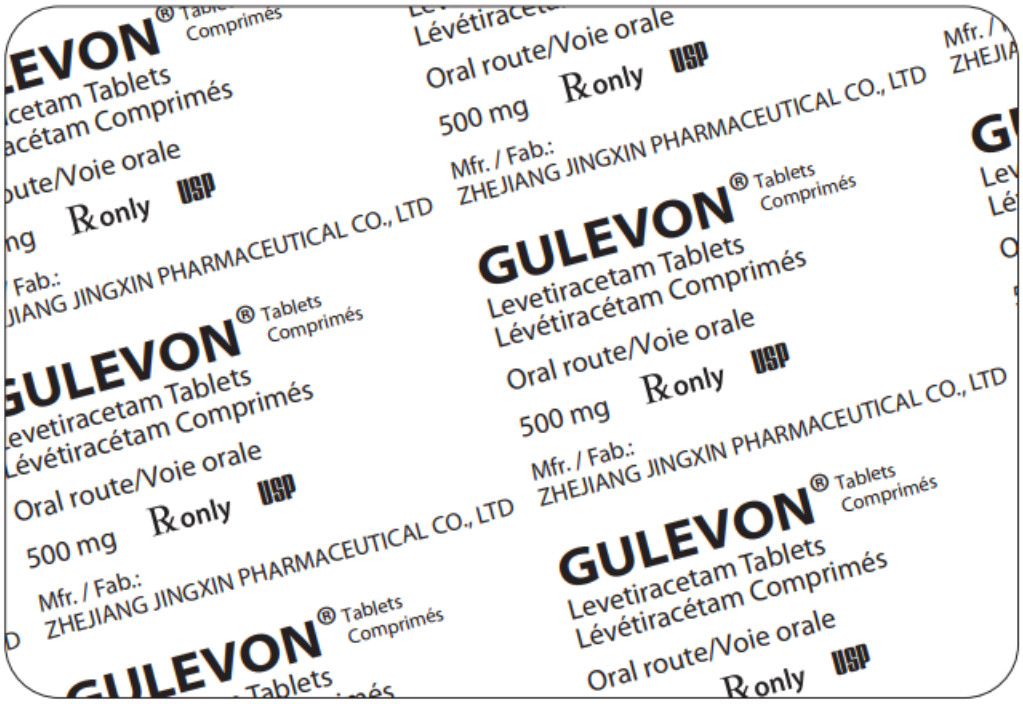
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

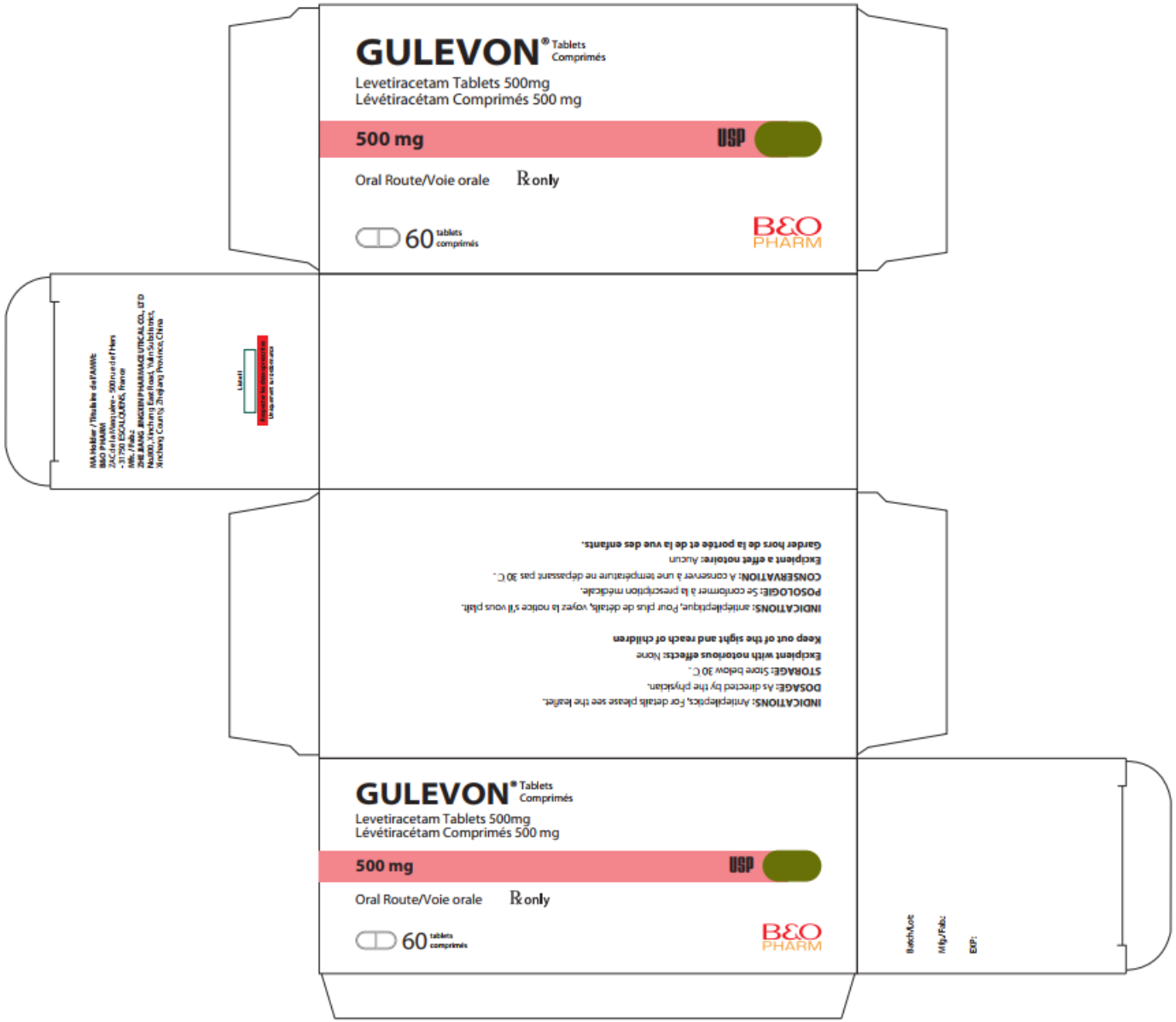
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label:



Effective date: 03/10/2022