THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CLONAPIN-2 (CLONAZEPAM USP 2 MG) TABLETS

Version number 1.0
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1. Introduction

CLONAPIN-2 tablets is a white to off white colour, round shaped, flat, break line on one side and plain on other side of uncoated tablet containing the 2 mg Clonazepam per tablet. The reference product is Rivotril 2 mg tablets of Roche. Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves. CLONAPIN-2 tablets is approved in Tanzania for use in all ages.

Product details

Registration number	TAN 23 HM 0285
Brand name	CLONAPIN-2
Generic name, strength, and form	Each tablet contains: Clonazepam 2 mg
ATC classification	N03AE – Benzodiazepine Derivatives
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Lincoln Pharmaceuticals Limited Trimul Estate, Khatraj, Taluka: Kalol, District: Gandhinagar Gujarat, India.
Local Technical Representative	Heko Pharmacy Limited, Plot 59, Tandamti na Sikukuu, Kariakoo, Dar es Salaam,

1.1 Assessment procedure

The application for registration of CLONAPIN-2 was submitted on 10/11/2021. The product underwent full assessment. Assessment was completed in 4 (four) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	White to off white colour, round shaped, flat, breakline on one side and plain on other side of uncoated tablet
Primary packing material	Alu/Alu Blister
Secondary packing materials	Carton
Shelf-life and storage condition	36 months, Do not store above 30 ^{o}C. Protect from light

Route of administration	Oral
Therapeutic indications	Clonapin is indicated, primarily as an adjunct or in refractory cases, in most forms of epilepsy especially absence seizures including atypical absence seizures; Lennox-Gastaut syndrome; myoclonic and atonic seizures. For infantile spasms (including West-Syndrome) and tonic-clonic seizures it is only indicated as an adjunct or in refractory cases.

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: CLONAPIN-2

Composition: Each tablet contains: Clonazepam 2 mg

Pack size: 3x10 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30 ^{o}C. Protect from light

Manufacturer address: physical address of release site

Unique identifier:

Special warnings/precautions or instructions for use: <This product contains Lactose>

The details of the primary pack include:

Brand name and strength: Not applicable

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Lincoln 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.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient

General Information

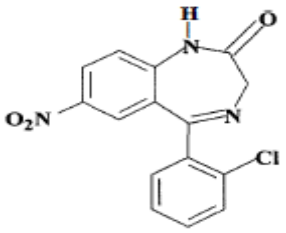
Clonazepam API is compendia in USP, BP, and Ph.Eur.

Molecular formula: $C_{15}H_{10}ClN_30_3$

Chemical name:

5-(a-Chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one.
OR
2H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenYl)-1,3-dihydro-7-nitro-.

Structure:



General properties

Clonazepam is a slightly yellowish, crystalline powder, which is practically insoluble in water and slightly soluble in methanol and ethanol. The solubility of the API across physiological pH has not been presented, however the API is known to be BCS class low soluble (BCS class II) hence PSD is critical. The API exhibit polymorphism however the manufacturer has demonstrated by several techniques including XRD that a uniform crystalline form is consistently manufactured. The API is non-hygroscopic in nature.

Manufacture

Clonazepam API manufacturer is Centaur Pharmaceuticals Private Limited, Plot No. 75, 76 & 76/1, Chikhloli MIDC, Ambemath (W), Dist. Thane 421 501, Maharashtra, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food and Drugs Administration, Gujarat Estate. Clonazepam 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification by IR, Melting Point, Loss on drying, Residue on Ignition, Limit of Clonazepam related Compound C, Related Compounds, Residual Solvents, Assay, Particle size, Tapped Density. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Clonazepam API is 60 months when packed in polyethylene bags (LD PE) with storage condition 'Store at room temperature'.

Quality of the Finished Pharmaceutical Product

Formulation

CLONAPIN-2 tablets is a white to off white colour, round shaped, flat, breakline on one side and plain on other side of uncoated tablet.

CLONAPIN-2 tablets contains the Clonazepam other ingredients listed here after: Microcrystalline cellulose, Croscarmellose Sodium Purified Talc, and Magnesium Stearate. 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. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturers are Lincoln Pharmaceuticals Limited, Trimul Estate, Khatraj, Taluka: Kalol, District: Gandhinagar Gujarat, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: Description, Identification, Average weight, Uniformity of dosage units (By Content uniformity)

Disintegration, Dissolution, Related Compound, Assay, 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 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 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 Alu/Alu blister with storage condition 'Do not store above 30 °C. Protect from light'.

Safety and efficacy information

Safety and efficacy of CLONAPIN-2 tablets was established through bioequivalence trial.

BE trial report number CLP_177_20 was submitted.

In case of BE:

<table>
<tr><td>Study title</td><td>'A randomized, open-label, two-treatment, two-period, two-sequence, single-dose, two-way crossover, comparative, bioequivalence study of Clonazepam Tablets USP 2 mg (Clopin) of Lincoln Pharmaceuticals Ltd., India. With compared with Klonopin® Tablets (containing 2 mg Clonazepam) of Hoffmann La Roche Inc., Distributed by Genentech, USA, Inc., in healthy, adult, human subjects under Fasting condition</td></tr>
<tr><td>Study design</td><td>A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover, oral bioequivalence study under fasting conditions with at least 21 Days washout period between each drug administration</td></tr>
<tr><td>Study site</td><td>Om Sai Clinical Research Pvt. Ltd
C. S. B. No. 379/1-6, Kamal Chowk,
Peth Bhang, Sangli – 416416,
Maharashtra, India</td></tr>
<tr><td>Study dates</td><td><table><tr><th>Activities</th><th>Dates</th></tr><tr><td>Period I (dosing)</td><td>11/6/2020 to 13/6/2020</td></tr><tr><td>Period II (dosing)</td><td>01/07/2020 to 03/07/2020</td></tr><tr><td>Analysis (start date)</td><td>11/08/2020</td></tr><tr><td>Analysis (completion date)</td><td>02/09/2020</td></tr></table></td></tr>
<tr><td>Primary objective</td><td>To demonstrate the bioequivalence between Test Product (T): Clonazepam Tablets USP 2 mg and Reference Product (R):</td></tr>
</table>

	Klonopin® Tablets (containing 2 mg Clonazepam) in normal, healthy, adult, human subjects, under fasting conditions	
Secondary objective	To monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).	
Number of participants	Planned-40 subjects Enrolled-40 subjects Dosed-40 subjects Withdrawn - 00 subject Bio-sample analyzed -40 subjects Pharmacokinetic and statistical data analyzed – 40 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 2 mg Batch number: CM0001 Expiry date: 12/2022	Strength: 2 mg Batch number: KP6902 Expiry date: 05/2020
Analytical method	High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte	
Statistical method	SAS® (SAS Institute Inc., USA) procedure	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

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, Clonazepam Tablets USP 2 mg (Clopin) of Lincoln Pharmaceuticals Ltd., India is equivalent and interchangeable with Klonopin® Tablets (containing 2 mg Clonazepam) of Hoffmann La Roche Inc., Distributed by Genentech, USA, Inc., 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. Clonazepam tablets 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