TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR NORMOPRESS (LOSARTAN POTASSIUM 50 MG) TABLETS

Version number 1.0
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1. Introduction

Normopress is a generic medicine of COZAAR (Losartan Potassium 50mg) Tablets of Merck Sharp and Dohme. Normopress is an antihypertensive medicine belonging to Angiotensin II Receptor Antagonists group. Losartan is a non-peptide angiotensin II antagonist with antihypertensive activity. Upon administration, losartan and its active metabolite selectively and competitively blocks the binding of angiotensin II to the angiotensin I (AT1) receptor. This blocks the vasoconstricting and aldosterone-secreting actions of angiotensin II, leading to a decrease in blood pressure. Angiotensin II, formed from angiotensin I by angiotensin-converting enzyme (ACE), stimulates the adrenal cortex to synthesize and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle. Normopress is approved in Tanzania for use in adults and in children and adolescents 6-18 years of age

1.1 Product details

Registration number	TAN 22 HM 0134
Brand name	Normopress
Generic name, strength and form	Losartan Potassium 50mg, Tablets
ATC classification	ATC code: C09CA01 Angiotensin II Receptor Antagonist
Distribution category	POM
Country of origin	Pakistan
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	M/s CCL Pharmaceuticals (Pvt.) Ltd 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan
Local Technical Representative	Name: Irfan Sohail Phone: +92 (42) 111 225 678 Fax: +92-42-35114382 Email: mail.ccl@cclpharma.com

1.2 Assessment procedure

The application for registration of Normopress was submitted on 2016 The product underwent full assessment. Assessment was completed in 5 rounds of evaluation. Normopress was registered on 13th April, 2022.

1.3 Information for users

Visual description of the finished product	White oval film coated tablet
Primary packing material	Alu-Alu blister
Secondary packing materials	Cardboard carton box
Shelf-life and storage condition	24 months
Route of administration	Oral

Therapeutic indications	Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age. Treatment of renal disease in adult patients with Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age. Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment. Treatment of chronic heart failure in adult patients when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure. Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

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: Normopress (Losartan Potassium 50 mg) Film coated tablets
Composition: Losartan Potassium 50 mg
Pack size: 1 x 10's tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store below 30°C, Protect from heat, sunlight & moisture
Manufacturer address: CCL Pharmaceuticals (Pvt.) Ltd., 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan

Unique identifier: NA
Special warnings/precautions or instructions for use: NA

The details of the primary pack include:
Brand name and strength: Normopress (Losartan Potassium 50 mg) Film coated tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: CCL Pharmaceuticals (Pvt.) 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

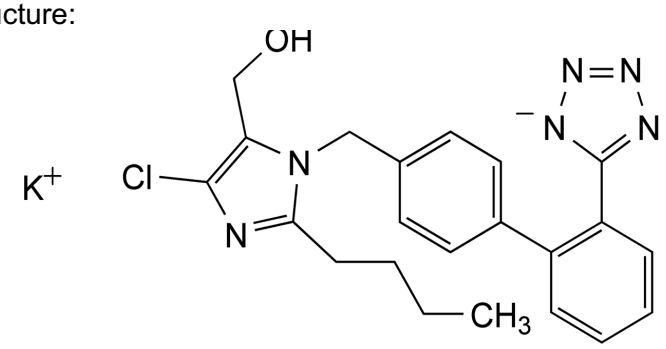
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Losartan Potassium API is compendia in USP/BP
Molecular formula: $C_{22}H_{22}ClKN_6O$
Chemical name: Potassium 5-[4′-[[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl]methyl]biphenyl-2-yl]tetrazol-1-ide.

Structure:



Physico-chemical properties of the API

Losartan Potassium is a white or almost white crystalline powder, which is freely soluble in water and in methanol, and slightly soluble in acetonitrile. It shows polymorphism and a single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterised

Manufacture

The API manufacturing site is Vasudha Pharma Chem Limited, Plot No. 79, J.N.Pharma City, Parawada, Visakhapatnam- 531021, Andhra Pradesh, India. The site complies with GMP requirements as evidenced by the GMP certificate issued by Government of Andhra Pradesh Drug Control Administration. Losartan Potassium 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: Description, solubility, Identification (by IR, UV and chemical test), water content (by KF), heavy metals, chromatographic purity (by HPLC), related substances, assay and residual solvents (by GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Losartan Potassium API is 36 months when packed in double low density polyethylene bags in HDPE drum and stored at below 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Normopress (Losartan Potassium 50 mg) tablets is a white oval film coated tablets. Normopress contains Losartan Potassium and other ingredients listed here after: Lactose, Sodium Starch, Glycol late, Povidone K-30, Magnesium Stearate, Isopropyl Alcohol and Opadry white-OY-C-7000A (Titanium Dioxide, Methanol, Methylene Chloride, Eudragit E-100, Isopropyl Alcohol, Polyethylene Glycol-6000). 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. Lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at M/s CCL Pharmaceuticals (Pvt.) Ltd., 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 22nd May, 2020

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per USP and ICHQ3B requirements. The parameters monitored during quality control are: Description, average weight, dissolution, disintegration, uniformity of dosage unit, identification, assay and related substances. 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 30°C ± 2ºC, 75% ± RH 5% for 24 months and 40°C ± 2ºC, 75% ± RH 5% for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu-Alu blister at below 30°C, Protect from heat, sunlight & moisture.

Safety and efficacy information

Safety and efficacy of Normopress (Losartan Potassium 50 mg) tablets was established through bioequivalence trial. BE trial report number BE/LST/001 was submitted.

Study title	A balanced, open label, randomized, crossover design, single centre, two treatment, two period, two sequence, single dose bioequivalence study of NORMOPRESS Tablet 50 mg (Losartan Potassium Tablet 50mg) of CCL Pharmaceuticals (Pvt) Ltd Vs COZAAR 50 mg Tablet (Losartan Potassium Tablet 50mg) of Merck Sharp and Dohme, in 24 + 2 (standby) normal, healthy, adult, male, human subjects under fasting conditions	
Study design	open label, two treatment, two period, two sequence, single dose bioequivalence study	
Study site	ICBio Clinical Research Pvt. Ltd. #16, ICBio Tower, Chikkabettahalli, Yelahanka Main Road, Vidyaranyapura, Bangalore – 560097, India	
Study dates	Study Initiation Date: 04/03/2016 Study Completion Date: 01/03/2016	
Primary objective	To assess the in vivo response of the dosage form with respect to extent of and rate of absorption of Losartan Potassium Tablet 50mg of CCL Pharmaceuticals (Pvt) Ltd and COZAAR (Losartan Potassium Tablet 50 mg) of Merck Sharp and Dohme	
Secondary objective	To monitor the safety and tolerability of a single dose of Te Losartan Potassium Tablets administered in healthy human adults	
Number of participants	26 (24 + 2 standby)	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 50 mg Batch number: FK 178 Expiry date: 08/2017	Strength: 50 mg Batch number: L10217 Expiry date: 02/2017
Analytical method	LC-MS/MS was used for estimation of Losartan and Losartan carboxylic acid (metabolite) in human plasma	
Statistical method	Complete the statistical method	

Efficacy results are summarized as follows:
Table 1: Summary of bioequivalence parameters for Losartan

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.hr/mL)	705.286	707.667	99.66	98.19 – 101.16	24	
$AUC_{0\text{-}inf}$ (ng.hr/mL)	721.039	730.525	98.70	97.17 – 100.25	24	
Cmax (ng/mL)	215.785	210.128	102.69	98.45 – 107.12	24	

Table 2: Summary of bioequivalence parameters for metabolite

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.hr/mL)	1120.493	1120.187	100.00	98.82 – 101.25	24	12.216
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1184.211	1189.915	99.52	98.36 – 100.70	24	11.959
Cmax (ng/mL)	219.210	223.119	98.25	95.85 – 100.71	24	12.277

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, NORMOPRESS Tablet 50mg (Losartan Potassium Tablet 50 mg) is equivalent and interchangeable with COZAAR 50mg Tablet (Losartan Potassium Tablet 50 mg) 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. NORMOPRESS Tablet 50mg (Losartan Potassium Tablet 50 mg) 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
NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label