

TMDA/DMC/MRE/F/016

Rev #:02



THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH



TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LOSACAR H 100/25 (LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE USP 100MG/25MG) AND LOSACAR H 50/12.5 (LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE USP 50MG/12.5MG) TABLETS

Version number 1.0

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1. Introduction

Losacar H 100/25 is a generic medicine of Losartan Potassium and Hydrochlorothiazide Tablets. Losacar H 100/25 is an antihypertensive medicine belonging to C09DA01- Agents acting on the renin-angiotensin system; Angiotensin II antagonists and diuretics group. Losacar H 100/25 exerts its activity by reducing blood pressure through inhibition of renin-angiotensin-aldosterone system. Losacar H 100/25 is approved in Tanzania for use in <adults, children, elderly etc>.

1.1 Product details

Registration number	Losacar H 100/25: TAN 20 HM 0333 Losacar H 50/12.5: TAN 20 HM 0391
Brand name	Losacar H 100/25 Losacar H 50/12.5
Generic name, strength and form	Losartan Potassium and Hydrochlorothiazide Tablets USP 100 mg/25 mg Losartan Potassium and Hydrochlorothiazide Tablets USP 50 mg/12.5 mg
ATC classification	C09DA01 - Agents acting on the renin-angiotensin system; Angiotensin II antagonists and diuretics
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	Cadila Healthcare Limited Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015 India E-Mail : rajeev.nanda@zyduscadila.com
Local Technical Representative	Abacus Pharma (A) limited, P.O. Box 12294, Dra es Salaam.

1.2 Assessment procedure

The application for registration of Losacar H 100/25 was submitted on 16/11/2018. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Losacar H 100/25 was registered on 25/09/2020.

The application for registration of Losacar H 50/12.5 was submitted on 16/11/2018. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Losacar H 50/12.5 was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Losacar H 100/25: White to off white capsule shaped, film coated tablets debossed with “Z32” on one side and plain on other side Losacar H 50/12.5: White to off white capsule shaped, film coated tablets debossed with “Z31” on one side and plain on other side
Primary packing material	Alu-Alu
Secondary packing materials	Carton Box of 3 Blisters of 10`s
Shelf-life and storage condition	24 months Store below 30°C
Route of administration	Oral
Therapeutic indications	Indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and nonfatal cardiovascular (CV) events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs

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 that is intended for long term use , the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Losacar H 100/25 , Losacar H 50/1.25

Composition: Losartan Potassium 100 mg and Hydrochlorothiazide 25 mg,

Losartan Potassium 50 mg and Hydrochlorothiazide 12.5 mg

Pack size: 3 ×10 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store up to 30°C

Manufacturer address: Cadila Healthcare Limited, Kundaim Industrial Estate,Plot No.203-213, Kundaim, Goa 403 115, INDIA

Unique identifier: NA

Special warnings/precautions or instructions for use: The product contains lactose.

The details of the primary pack include:

Brand name and strength: Losacar H 100/25 , Losacar H 50/12.5

Manufacturing details: batch number, expiry date

Name of manufacturer: Zydus Cadila

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)

Losartan Potassium

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

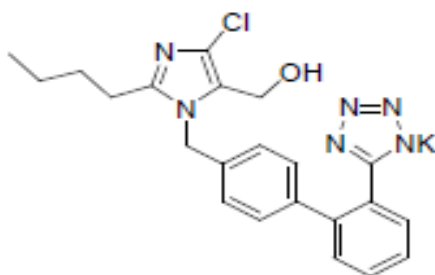
General properties

Losartan Potassium API is compendia in USP/BP.

Molecular formula: $C_{22}H_{22}ClKN_6O$

Chemical name: 2-Butyl-4-chloro-1-[p-(o-1H-tetrazol-5 ylphenyl)benzyl]imidazole-5-methanol, monopotassium salt

Structure:



Critical physico-chemical properties of the API were Freely soluble in Water and Methanol and exhibits polymorphism (form I to IV). Polymorph I is consistently manufactured.

Manufacture

The API manufacturing site, Zhejiang Huahai Pharmaceutical Co., Ltd, Chuannan site, Coastal Industrial Zone, Duqiao, Linhai, Zhejiang, 317016, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Italian Medicine Agency. 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, responds to the test of potassium, water content, heavy metals organic impurities, assay, clarity of solution, ph, particle size, polymorphism. 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 60 months when packed in low density polyethylene bag and stored at 25°C.

Hydrochlorothiazide

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

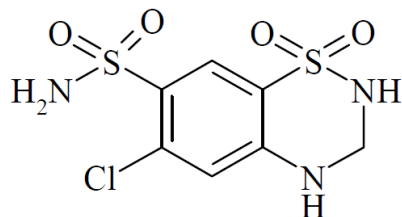
General properties

Hydrochlorothiazide API is compendia in USP/BP.

Molecular formula: $C_7H_8ClN_3O_4S_2$

Chemical name: 6 - chloro-3, 4 - dihydro - 2 H-1, 2, 4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Structure:



Critical physico-chemical properties of the API were very slightly soluble in water and freely soluble in sodium hydroxide solution. It exists in four polymorphic forms where form I is consistently manufactured from the site.

Manufacture

The API manufacturing site, CTX Lifesciences Pvt. Ltd., Block No. 251-252, Sachin- Magdalla Road GIDC, Sachin, Surat – 394 230 Gujarat, INDIA was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>. Hydrochlorothiazide 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, loss on drying, residue on ignition, chloride, organic impurities, assay, selenium, residual solvent and particle size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Hydrochlorothiazide API is 60 months when packed in polyethylene ldp bags and stored at 25°C.

Quality of the Finished Pharmaceutical Product

Formulation

Losacar H 100/25 is a white to off white capsule shaped, film coated tablets debossed with “Z32” on one side and plain on other side. Losacar H 50/12.5 is a white to off white capsule shaped, film coated tablets debossed with “Z31” on one side and plain on other side. Losacar H contains Losartan Potassium and Hydrochlorothiazide and other ingredients listed here after lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, isopropyl alcohol, purified water, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate, opadry white and purified water. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, lactose monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Cadila Healthcare Limited, Kundaim Industrial Estate, Plot No.203-213, Kundaim, Goa 403 115, INDIA. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 22nd and 23th August 2019.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, dissolution, average weight, uniformity of dosage units (by content uniformity), assay, organic impurities, water content, microbial test and hardness. 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 30°C ± 2°C/75% ± 5% RH for 24 months and 40°C ± 2°C/75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu-Alu Blister pack at below 30°C.

Safety and efficacy information

Losacar H 100/25 tablets

Safety and efficacy of Losacar H 100/25 was established through bioequivalence trial. BE trial report number US/06/016 was submitted.

In case of BE:

Study title	An Open Label, Randomized, Two Period, Two Sequence, Crossover, Bioequivalence Study of Two Formulations of Losartan Potassium and Hydrochlorothiazide Tablets 100 mg /25 mg in Health Adult Human subjects under fasting condition	
Study design	An Open Label, Randomized, Two Period, Two Sequence, Crossover, Bioequivalence Study	
Study site	Accutest Research Laboratories (I) Pvt. Ltd A-31, M.I.D.C, T.T.C Industrial Area, khairane, Navi Mumbai-400709, INDIA	
Study dates	Clinical phase; 26/April/ 2006 - 02/June/2006	
Primary objective	to demonstrate bioequivalence between the two formulations	
Secondary objective		
Number of participants	60	
Monitored parameters	C _{max} , AUC _t and AUC _i	
Investigational medicinal products	Test Product Losacar H 100/25 of Cadila Healthcare Limited, India	Reference product HYZAAR® 100-25 of Merck & Co. Inc., USA
	Strength: Losartan Potassium-100 mg Hydrochlorothiazide 25 mg Batch number: ME 4383 Expiry date:	Strength: Losartan Potassium-100 mg Hydrochlorothiazide 25 mg Batch number: R2940 Expiry date: June 2008
Analytical method	APLC/MS/MS	
Statistical method	SAS® statistical software (Version 8.4; SAS 39 Institute Inc, USA)	

Efficacy results are summarized as follows:

Losartan

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)

AUC _{0-t} (units)	1237.34	1215.55	101.71%	98.01 %	1	1.692
AUC _{0-inf} (units)	1266.26	1249.54	101.25%	97.56 %	1	1.694
C _{max} (units)	629.94	658.73	95.54%	84.47 %	1	6.189

Hydrochlorothiazide

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC _{0-t} (units)	1038.55	937.38	110.94 %	105.85 %	1	2.212
AUC _{0-inf} (units)	1139.87	1033.72	110.42 %	105.79 %	1	1.988
C _{max} (units)	157.34	145.48	108.19 %	102.02 %	1	3.797

The acceptance limits of 80 – 125% are met by the AUC and C_{max} values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Losacar H 100/25 is equivalent and interchangeable with HYZAAR® 100-25 under acceptable in vivo experimental conditions.

Losacar H 50/12.5 tablets

Safety and efficacy of Losacar H 50/12.5 tablets was established through biowaiver application. Comparative dissolution report number <number> was submitted.

The biowaiver was approved based on additional strength.

Losacar H 50/12.5 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Losacar H 50/12.5 was compared to Losacar H 100/25. Less than 85% of the labelled amount of Losartan potassium and Hydrochlorothiazide 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. Losacar H 100/25 and Losacar H 50/12.5 are 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

Locasar H 100/25



<p style="text-align: center;">LOSACAR H 100/25</p> <p>Each film coated tablet contains: Losartan Potassium USP 100mg Hydrochlorothiazide USP 25mg Color: Titanium Dioxide The product contains Lactose.</p> <p>STORE UPTO 30°C. PROTECT FROM LIGHT. KEEP OUT OF REACH OF CHILDREN. Dosage: As directed by the Physician.</p> <p>8 9 0 1 1 2 0 0 1 4 4 9 1</p> <p>Mfg. Lic. No.: 186 Manufactured by: Cadila Healthcare Limited, Kundaim Industrial Estate, Plot No. 203-213, Kundaim, Goh - 403 115, INDIA.</p>	<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>
<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>	<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p>
<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>	<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>
<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>	<p style="text-align: center;">LOSACAR H 100/25</p> <p style="text-align: center;">100mg/25mg</p> <p style="text-align: right;">Zydus Cadila</p>

Locasar H 50/12.5



<p>LOSACAR H 50/12.5</p> <p>Each film coated tablet contains: Losartan Potassium USP 50mg Hydrochlorothiazide USP 12.5mg Color: Titanium Dioxide</p> <p>The product contains Lactose.</p> <p>STORE UPTO 30°C, PROTECT FROM LIGHT. KEEP OUT OF REACH OF CHILDREN.</p> <p>Dosage: As directed by the Physician.</p> <p>Manufactured by: Cadila Healthcare Limited, Kundaim Industrial Estate, Plot No, 203-213, Kundaim, Goa - 403 115, INDIA.</p> <p>Mfg. Lic. No.: 186</p>  <p>8 9 0 1 1 2 0 1 0 1 4 4 7 7</p>	<p>LOSACAR H 50/12.5</p> <p>50mg/12.5mg</p> <p>Zydus Cadiila</p>
<p>LOSACAR H 50/12.5</p> <p>50mg/12.5mg</p> <p>Zydus Cadiila</p>	
<p>3 x 10 Tablets</p> <p>PRESCRIPTION DRUG</p> <p>Losartan Potassium and Hydrochlorothiazide Tablets USP 50mg/12.5mg LOSACAR H 50/12.5</p> <p>50mg/ 12.5mg</p> <p>Zydus Cadiila</p>	

Effective date: 03/10/2022

