THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LASTAVIN 160 (VALSARTAN 160MG) FILM COATED TABLETS

Version number 1.0
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1. Introduction

Lastavin 160 film coated tablet contains valsartan 160mg. Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT 1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT 1 receptor blockade with valsartan may stimulate the unblocked AT 2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT 1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. Lastavin 160 film coated tablet is approved in Tanzania for use in children and adolescents 6 to 18 years of age, and adults (including the elderly).

Product details

Registration number	TAN 23 HM 0261
Brand name	Lastavin 160
Generic name, strength, and form	Valsartan 160 mg
ATC classification	C09CA03- The angiotensin II receptor blocker (ARB) family
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (W), Mumbai 400067, India
Local Technical Representative	ASTRA PHARMA (T) LTD. Plot no-12, Vingunguti Industrial Area, Nyerere Road, opp: Pepsi tanzania Ltd, Dar -Es- Salaam, Tanzania.

1.1 Assessment procedure

The application for registration of Lastavin 160 was submitted in 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	Pink coloured, circular shaped, biconvex, film coated tablets, plain on one side and breakline on other side
Primary packing material	Alu-Alu blister
Secondary packing materials	Printed carton box

Shelf-life and storage condition	30 months, Do not store above 30°C, Protect from light.
Route of administration	Oral
Therapeutic indications	Hypertension • Treatment of essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age. Recent myocardial infarction • Treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction. Heart failure •Treatment of adult patients with symptomatic heart failure when ACE-inhibitors are not tolerated or in beta-blocker intolerant patients as add-on therapy to ACE-inhibitors when mineralocorticoid receptor antagonists cannot be used

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: Lastavin 160

Composition: Valsartan 160 mg

Pack size: 3x10 tablets

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

Storage conditions: Do not store above 30°C, Protect from light.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use:

The details of the primary pack include:

Brand name and strength: Lastavin 160

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Ajanta Pharma 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 Ingredients

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

General Information

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

Molecular formula: $C_{24}H_{29}N_5O_3$

Chemical name:

N-[p-(o-1H-tetrazol-5-ylphenyl) benzyl]-N- valeryl- L-valine
[Or]

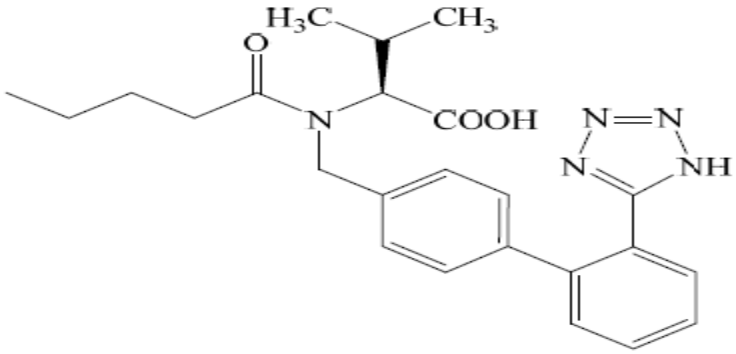
L-Valine, N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]
[Or]

(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-Npentanoyl- N-[2'-(1H-tetrazol-5-yl)-biphenyl-4 ylmethyl] amine

[Or]

N-(1-Oxopentyl)-N-[[2'-(1H-tetrazole-5-yl) [1, 1'- biphenyl]-4-yl] methyl]-L-Valine

Structure:



General properties

The active substance is white to almost white hygroscopic powder, freely soluble in anhydrous ethanol, sparingly soluble in dichloromethane, practically insoluble in water. The substance shows polymorphism and stereoisomerism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

Valsartan is a class II substance in the BCS classification system. It has a low aqueous solubility. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution.

Manufacture

Valsartan API manufacturer is Dr. Reddy's Laboratories Limited, Chemical Technical Operations-Unit VI, APIIC Industrial Estate, Pydibhimavaram, Ranasthalam Mandal, Srikakulam District, Andhra Pradesh, India –532409. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Drugs Control Administration, Andhra Pradesh, India. Valsartan 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

Specifications

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: appearance, solubility, identification by HPLC and IR, appearance of solution, pH, absorbance, polymorphism, related substances, nitrosamine impurities residue on ignition, particle size distribution, water, assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The retest period of Valsartan API is 60 months when packed in original container with storage condition 'Preserve in tight light-resistant containers at 25°C. Protect from moisture and heat'.

Quality of the Finished Pharmaceutical Product

Formulation

Lastavin 160 film coated tablet is a pink coloured, circular shape, biconvex, film coated tablets, plain on one side and breakline on other side.

Lastavin 160 film coated tablet contains the Valsartan and other ingredients listed here after: microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, povidone, purified water, magnesium stearate, Instacoat EHP 250 A10R00391 pink (titanium dioxide, yellow iron oxide, red iron oxide). 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 Ajanta Pharma Limited, B-4-5-6, MIDC Industrial Area, Paithan, Aurangabad, 431148, Dist: Aurangabad, Maharashtra, 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 in-house standards and ICH requirements. The parameters monitored during quality control are: appearance, identification of API and colourants, water content, disintegration, uniformity of dosage units, dissolution, related substances, assay, and microbial quality. 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: 35 ± 5% RH for 30 months and 40± 2°C & RH: 25% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 30 months when stored in original container with storage condition ‘Do not store above 30°C, Protect from Light’.

Safety and efficacy information

Safety and efficacy of Lastavin 160 film coated tablet was established through a bioequivalence trial.

BE trial report number BIOS/2021/113 was submitted.

Study title	A randomized, open label, balanced, two treatments, two period, two sequence, two ways, cross-over, single oral dose, bioequivalence study of Valsartan Tablets USP 160 mg of Ajanta

	Pharma Limited, India with Diovan® 160 mg (Valsartan Tablets 160 mg) distributed by Novartis Pharmaceuticals Corp. - USA in healthy adult human male subjects under fasting conditions.	
Study design	Comparative randomised, single dose, two-way cross over open label study under fasting condition	
Study site	Bio Scientific Research Laboratories (I) Pvt. Ltd. BIOS HOUSE, Plot No. 106/3, Aries Compound, Opp. Thakur Mall, S V Road, Mira Road, Thane 401104, India	
Study dates	Period I (dosing): 22/09/2021 to 24/09/2021 Period II (dosing): 30/09/2021 to 02/10/2021 Analysis (start date): 18/10/2021 Analysis (completion date): 31/10/2021 Statistical Analysis: 11/11/2021	
Primary objective	To investigate the bioequivalence of test product relative to reference product after a single oral dose administration of Valsartan to healthy adults under fasting conditions	
Secondary objective	To monitor the safety and tolerability of a single dose of Valsartan tablets when administered in 56 healthy adult human subjects under fasting condition	
Number of participants	Planned-56subjects Enrolled-56 subjects Dosed-56 subjects Withdrawn - 01 subject Bio-sample analyzed -55 subjects Pharmacokinetic and statistical data analyzed – 55 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 160 mg Batch number: PA12091 Expiry date: 12/2023	Strength: 160 mg Batch number: AN7896C Expiry date: 08/2023
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® procedure	

Efficacy results are summarized as follows:

Geometric Means and 90% Confidence Interval for all the subjects' data of Valsartan(N=55)

Parameters	*Geometric mean		% Ratio	90 % CI for Log-transformed	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max} (ng/mL)	5140.161	5049.881	101.79	91.95	112.68
AUC_{0-t} (ng.hr /mL)	34670.099	34155.456	101.51	93.42	110.30
AUC_{0-inf} (ng.hr /mL)	35825.212	35307.039	101.47	93.52	110.09

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, Valsartan Tablets 160 mg of Ajanta Pharma Limited, India is equivalent and interchangeable with Diovan® 160 mg (Valsartan Tablets 160 mg) distributed by Novartis Pharmaceuticals Corp. - USA 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. Lastavin 160 film coated tablet 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