THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ADERAN 8 (CANDESARTAN CILEXETIL 8 MG) TABLETS

Version number 1.0
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1. Introduction

Aderan 8 is a generic medicine of Atacand 8 mg of AstraZeneca. Aderan 8 contains Candesartan cilexetil. Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity. Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (AT1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration. Aderan 8 is approved in Tanzania for use in adults only.

Product details

Registration number	TAN 23 HM 0269
Brand name	Aderan 8
Generic name, strength, and form	Each uncoated tablet contains Candesartan cilexetil 8 mg
ATC classification	Angiotensin II antagonists Antihypertensive ATC Code: C09CA06
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Ajanta Pharma limited Ajanta House, Charkop Kandivli (West) Mumbai- 400067 India
Local Technical Representative	Astra pharma (T) Limted Plot no-12, Vingunguti Industrial Area Nyerere Road, opp: Pepsi Tanzania Ltd, Dar -Es – Salaam

1.1 Assessment procedure

The application for registration of Aderan 8 was submitted on 29/03/2022. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Dark brownish pink coloured, slightly mottled, circular, biconvex, uncoated tablets, with ‘CA2’ engraved on one

	side and break line on other side
Primary packing material	Alu-Alu Pack
Secondary packing materials	Printed carton box
Shelf-life and storage condition	36 months, Do not above 30°C
Route of administration	Oral
Therapeutic indications	•For the treatment of primary hypertension in adults. •For the treatment in children and adolescents aged 6 to <18 years. •For the treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) when Angiotensin Converting Enzyme (ACE)-inhibitors are not tolerated or as add-on therapy to ACE-inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated. The medicine should be given under expert supervision.

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: Aderan 8

Composition: Each uncoated tablet contains Candesartan cilexetil 8 mg

Pack size: 30 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: Aderan 8

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

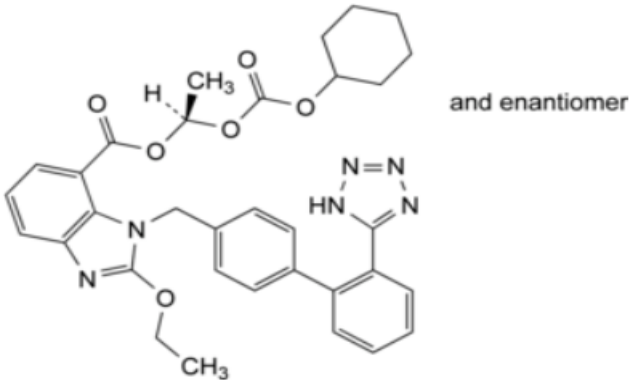
Candesartan cilexetil API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{33}H_{34}N_6O_6$

Chemical name:

(1RS)-1-[[(Cyclohexyloxy)carbonyl] oxy] ethyl2-ethoxy-1-[[2′-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate.

Structure:



General properties

The active substance is a white to off-white powder, which is insoluble in water and isopropyl alcohol, slightly soluble in methanol and sparingly soluble in 0.1N NaOH. Candesartan cilexetil has one chiral centre and exists in three polymorphic forms (I, II and amorphous).

Manufacture

Candesartan cilexetil API manufacturer is Mylan Laboratories Limited (Unit 7), Plot No.14,99 & 100, IDA, Pashamylaram Phase-II Patancheru, Sangareddy, District -502307, Telangana, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Government of Telangana. Candesartan cilexetil 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 (IR and HPLC), residue on ignition, organic impurities, nitrosamine impurities (N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosoethyl isopropylamine (NEIA), N-nitrosodiisopropylamine (NDIA)), water content, assay, residual solvents (GC), 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 Candesartan cilexetil API is 60 months when packed in polyethylene bag (LDPE), twisted and tied with plastic fastener and stored in tight containers.

Quality of the Finished Pharmaceutical Product

Formulation

Aderan 8 is a dark brownish pink coloured, slightly mottled, circular, biconvex, uncoated tablets, with 'CA2' engraved on one side and break line on other side.

Aderan 8 contains the Candesartan cilexetil and other ingredients listed here after: polyethylene glycol, corn starch, lactose monohydrate, ferric oxide red, hydroxypropyl cellulose, carboxymethylcellulose calcium, magnesium stearate, purified water. 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 monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturer is Ajanta Pharma Limited, Mirza-Palashbari Road, Village Kokjhar, Kamrup (R), Guwahati, Assam-781128. 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 of API and colourant, average weight, uniformity of weight, diameter, tablet breaking force, friability, disintegration time, water content, dissolution, uniformity of dosage units by content uniformity, organic impurities, assay, and microbiological purity. 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 24 months when stored in Alu-Alu blister pack with storage condition 'Do not above 30°C'

Safety and efficacy information

Safety and efficacy of <brand name> was established through <bioequivalence trial/biowaiver application/clinical trial>.

<BE trial/comparative dissolution> report number <number> was submitted.

In case of BE:

Study title	
Study design	
Study site	

Study dates		
Primary objective		
Secondary objective		
Number of participants		
Monitored parameters		
Investigational medicinal products	Test Product	Reference product
	Strength: Batch number: Expiry date:	Strength: Batch number: Expiry date:
Analytical method		
Statistical method		

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, <brand name> is equivalent and interchangeable with <comparator>under acceptable in vivo experimental conditions.

In case of biowaiver

The biowaiver was approved based on <BCS classification/additional strength>.

<Brand name> fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of <Brand name, strength, form> was compared to <comparator name, strength and form>.<At least/less than> 85% of the labelled amount of <molecule> had dissolved in all three media. Therefore, <confirming similarity/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. Aderan 8 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: