THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR KARDAM 10 (AMLODIPINE BESILATE EQUIVALENT TO AMLODIPINE 10 MG) TABLETS

Version number 01

03 January, 2022

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1. Introduction

KARDAM 10 is a generic medicine of Novartis® 10 mg Tablets. KARDAM 10 is a antihypertensives medicine belonging to Selective Calcium channel blockers, dihydropyridine derivative group. Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements. KARDAM 10 is approved in Tanzania for use in adults and children aged between 6-17 years

1.1 Product details

Registration number	TAN 21 HM 0417
Brand name	KARDAM 10
Generic name, strength and form	Amlodipine Besilate, 10 mg, Tablets
ATC classification	ATC code: C08CA01
Distribution category	POM
Country of origin	India
Associated product	KARDAM 5 (Amlodipine Besilate equivalent to Amlodipine 5mg) Tablets
Marketing Authorization Holder	Aurobindo Pharma Limited Plot No.2, Maitrivihar, Ameerpet, Hyderabad, Zip Code: 500 038, Telangana State, India
Local Technical Representative	Generic & Specialities limited, P. O. Box 1469, Dar es Salaam

1.2 Assessment procedure

The application for registration of KARDAM 10was submitted on DD/MM/2020. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation. KARDAM 10 was registered on 09 October 2021.

1.3 Information for users

Visual description of the finished product	White to off-white, flat, bevel edged round uncoated tablets, debossed with ‘C’ on one side and ‘59’ on the other side
Primary packing material	PVC-PVdC/ALU blisters
Secondary packing materials	Cardboard carton box
Shelf-life and storage condition	36 months, Do not Store above 30^{o}C
Route of administration	Oral

Therapeutic indications	Hypertension Chronic stable angina pectoris Vasospastic (Prinzmetal's) angina

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: KARDAM 10

Composition: Amlodipine Besilate equivalent to Amlodipine 10mg

Pack size: 3 x 10's

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not Store above $30^{o}C$

Manufacturer address: Aurobindo Pharma Limited, Unit-XV, Plot No. 17 A, E. Bonangi (V), Jawaharlal Nehru Pharma City, Parawada (M), Visakhapatnam Dist, Andhra Pradesh. INDIA

Unique identifier: NA

Special warnings/precautions or instructions for use: Refer the pack insert (please read the accompanying instructions before use).

The details of the primary pack include:
Brand name and strength:
Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Aurobindo 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.
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)

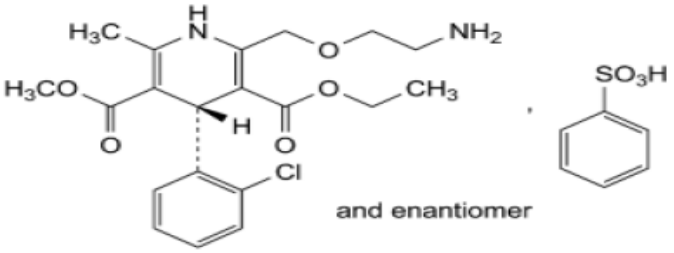
Information on quality of the API was submitted in form of CEP

General information
Amlodipine API is compendia in USP/BP/JP

Molecular formula: $C_{26}H_{31}ClN_2O_8S$

Chemical name: 2-[(2-amino ethoxy)-methyl]-4-(2-chloro phenyl)-1,4-dihydro-6-methyl-3,5-pyridine dicarboxylic acid 3-ethyl 5-methyl ester benzene sulphonate

Structure:



Physico-chemical properties of the API
Amlodipine appears as white or almost white powder, non-hygroscopic, slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol. It is optically active as it possesses one chiral center. The monograph is for the racemic mixture.

Amlodipine Besilate shows polymorphism/pseudo polymorphism. It has been reported in the literature that Amlodipine Besilate exists in different hydrates and anhydrates forms. Aurobindo Pharma limited manufactures crystalline anhydrous Besilate salt.

Manufacture
The API manufacturing sites, Aurobindo Pharma Limited, Unit – VIII, Survey.No: 10 &13, Gaddapotharam(Village), IDA – Kazipally, Jinnaram (Mandal), Medak (District), Telangana state, India and Aurobindo Pharma Limited, Unit – XIV, Plot No.17, E-Bonangi Village, Jawaharlal Nehru Pharma City, Parawada MandaI, Visakbapatnam District, Andhra Pradesh, India were noted to comply with GMP requirements as evidenced by the GMP certificate issued by Drug Control Administration, government of Telangana (DCA) and Drug Control Administration, government of Andhra Pradesh. Amlodipine Besilate 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 BP standards and ICHQ3A. The parameters monitored during quality control are: appearance (visual), solubility, identification (IR and optical rotation), related substances (HPLC), water content (Karl fisher), sulfate ash, assay (HPLC), bulk density,

residual solvents (GC), particle size distribution, microbial contamination. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Amlodipine API is 36 months when packed in original container and stored at 25ºC

Quality of the Finished Pharmaceutical Product

Formulation
KARDAM 10 is a white to off-white, flat, bevel edged round uncoated tablets, debossed with 'C' on one side and '59' on the other side. KARDAM 10 contains Amlodipine Besilate equivalent to Amlodipine and other ingredients listed here after: Cellulose microcrystalline, Calcium hydrogen phosphate anhydrous, Sodium starch glycolate (type A) and Magnesium stearate. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities.

Manufacture
The finished product was manufactured at Aurobindo Pharma Limited, Unit-XV, Plot No. 17 A, E. Bonangi (V), Jawaharlal Nehru Pharma City, Parawada (M), Visakhapatnam Dist, Andhra Pradesh, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 24/10/2019.

Specifications
The FPP is compendia in BP. The manufacturer controls the quality of the finished product as per reference monograph BP, in-house and ICHQ3B requirements. The parameters monitored during quality control are: appearance (visual), Identification (HPLC, TLC), average weight, assay (HPLC), dissolution, Uniformity of dosage units, related substance, water content (KF), disintegration and 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 ºC, 75% RH condition for 36 months and 40 ºC, 75% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in PVC- PVdC/Alu blister at below 30ºC

Safety and efficacy information

KARDAM 10 (10 Amlodipine (as Besilate)) tablet is generic product which is already registered by in the countries recognized by authority as they have stringent regulatory authorities (Spain and Portugal). In this context, re-assessment of this part is not considered as necessarily required.

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. KARDAM 10 (10 Amlodipine (as Besilate)) 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

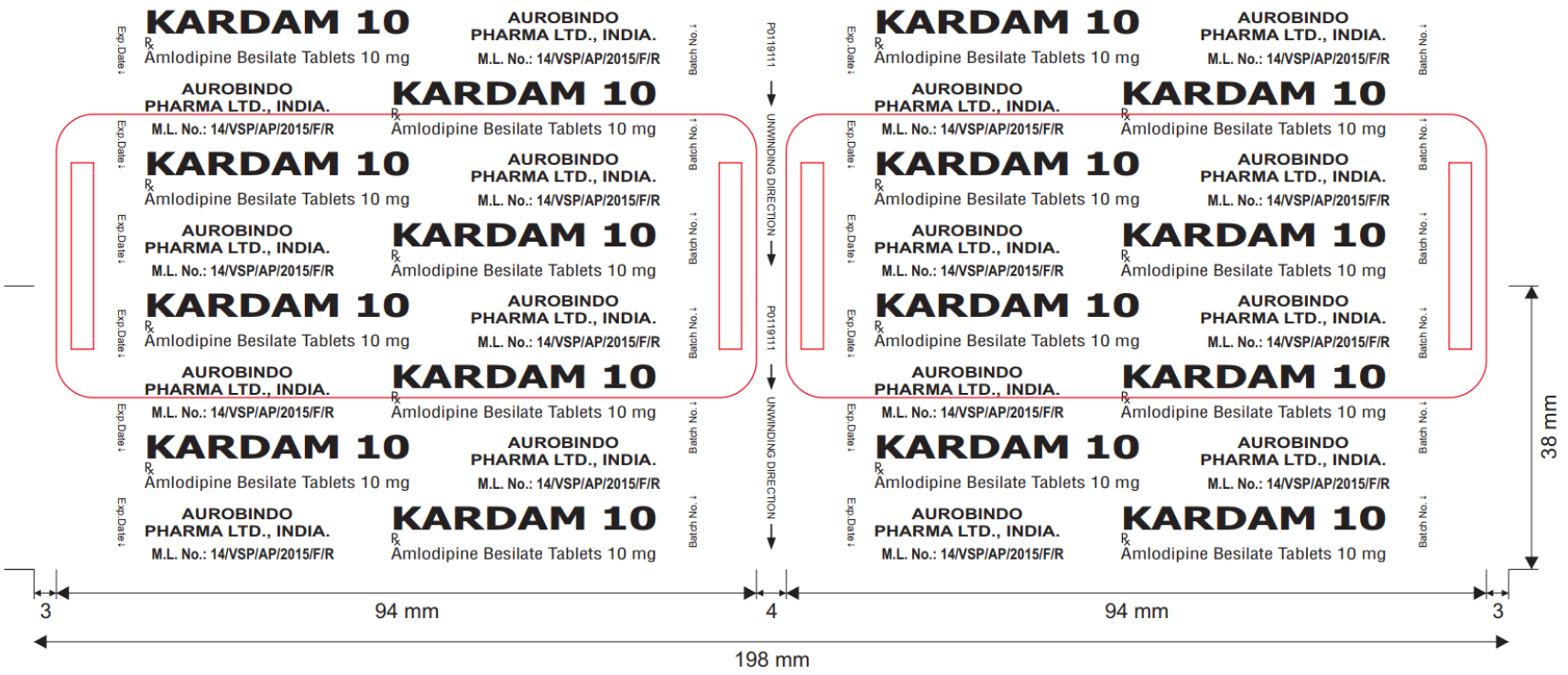
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

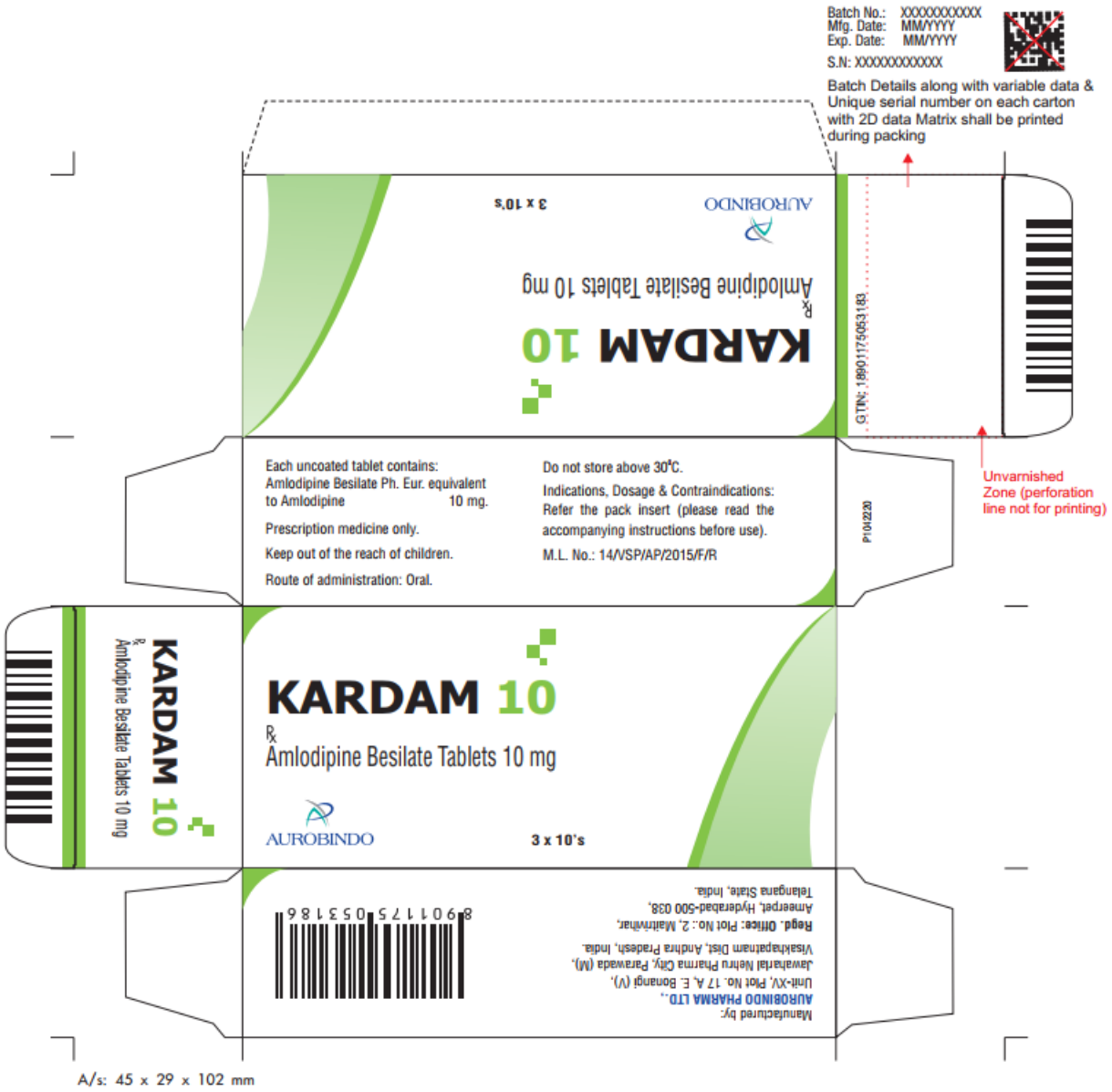
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label



Effective date: 03/10/2022