TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR AMLOVIE 5 (AMLODIPINE 5 MG) TABLETS

Version number 1.0

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1. Introduction

Amlovie 5 is a generic medicine of Novartis® 10 mg Tablets Amlovie 5 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. Amlovie 5 is approved in Tanzania for use in <adults and children aged between 6-17 years

1.1 Product details

Registration number	TAN 21 HM 023**6**
Brand name	Amlovie 5
Generic name, strength and form	Amlodipine, 10 mg, Tablets
ATC classification	ATC code: C08CA01
Distribution category	POM
Country of origin	Portugal
Associated product	Amlovie 5 (Amlodipine Besylate equivalent to Amlodipine 5mg) Tablets
Marketing Authorization Holder	Dafra Pharma GmbH Miihlenberg 7,4052 Basel Switzerland E-Mail: regulatory@dafra.be
Local Technical Representative	Harleys (T) Limited Dar es salaam Tanzania

1.2 Assessment procedure

The application for registration of Amlovie 5 was submitted on 2nd January 2020. The product underwent full and joint EAC assessment. Assessment was completed in 2 rounds of evaluation. Amlovie 5 was registered on 3rd June 2021

1.3 Information for users

Visual description of the finished product	White to almost white, oblong-shaped tablet with a score on one side of the tablet
Primary packing material	PVC-PVDC/ALU blisters
Secondary packing materials	Cardboard carton box
Shelf-life and storage condition	36 months, Store below 30ºC
Route of administration	Oral
Therapeutic indications	• Essential hypertension • Chronic stable and vasospastic anginal pectorisVasospastic (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 and French.

Details in the secondary pack label include:
Brand name: Amlovie 5

Composition: Amlodipine Besylate equivalent to Amlodipine 5mg

Pack size: 3 x 10's

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30ºC

Manufacturer address: Bluepharma – Indústria Farmacêutica S.A., S. Martinho do Bispo, Coimbra, 3045-016, Portugal

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

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

Name of manufacturer: Bluepharma - Indústria Farmacêutica S.A.

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)

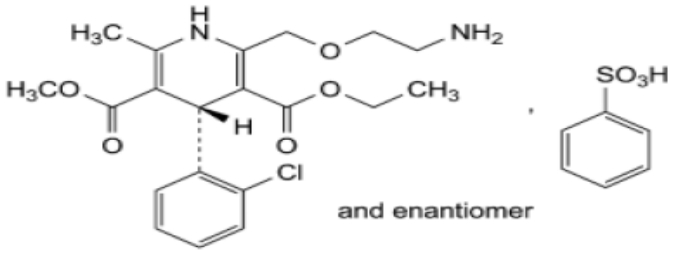
Information on quality of the API was submitted in form of CEP

General information
Amlodipine besilate – this salt is described in EP/BP/USP

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

Chemical name: 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.

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. Amlodipine Besylate exhibits polymorphism, it has two polymorphic forms, one is crystalline form and the other is Amorphous form. API manufacturer produces crystalline anhydrous Amlodipine Besylate which is characterized by the pXRD. Amlodipine Besylate is a racemic compound

Manufacture

The API manufacturing site, Hetero Drugs Limited, Hetero Corporate, 7-2-A2, Industrial Estates Sanath Nagar, 500018 Hyderabad, Telengana, India was noted to comply with GMP requirements as evidenced by the GMP certificate issued by Drug Control Administration government of Telangana (DCA). Amlodipine Besylate 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, HPLC and optical rotation), related substances (HPLC), water content (Karl fisher), sulfate ash, assay (HPLC), content of methyl benzene sulphonate (HPLC) residual solvents (GC), particle size distribution, besylate ion content by titration. 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 60 months when packed in double polyethylene bags, the outer bag is black, placed in a polyethylene drum and stored at 25ºC

Quality of the Finished Pharmaceutical Product

Formulation

Amlovie 5 is a white to almost white tablets of oblong shape with a score on one side of the tablets. Amlovie 5 contains Amlodipine Besylate equivalent to Amlodipine and other ingredients listed here after: Cellulose microcrystalline, Calcium hydrogen phosphate dihydrate, 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 6th in terms of function and quantities.

Manufacture

The finished product was manufactured at Bluepharma Indústria Farmacêutica, S.A Martinho do Bispo 3045-016 Coimbra, Portugal. The compliance of the site to TMDA GMP standards was confirmed through desk-review on date of GMP compliance.

Specifications

The FPP is an in-housed specification based on compendial monograph and ICH. The manufacturer controls the quality of the finished product as per reference monograph, in-house and ICHQ3B requirements. The parameters monitored during quality control are: appearance (visual), Identification (HPLC-RT, HPLC-PDA), 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 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 30ºC

Safety and efficacy information

Safety and efficacy of Amlovie 5 was established through biowaiver application. comparative dissolution was submitted.

The biowaiver was approved based on additional strength.

Amlovie 5 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Amlovie 5 (Amlodipine 5 mg) tablets were compared to Amlovie 10 (Amlodipine 10 mg) of Bluepharma – Indústria Farmacêutica, S.A. At least 85% of the labelled amount of Amlodipine had dissolved in all three media after 15 minutes. Therefore, confirming similarity

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. Amlovie 5 (Amlodipine 5 mg) 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

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label