TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR AMLOVIE 10 (AMLODIPINE 10MG) TABLETS

Version number 1.0

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1. Introduction

Amlovie 10 is a generic medicine of Novartis® 10 mg Tablets Amlovie 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. Amlovie 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 0237
Brand name	Amlovie 10
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 10 was submitted on 2nd January 2020. The product underwent full and joint EAC assessment. Assessment was completed in 2 rounds of evaluation. Amlovie 10 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 Fresh.

Details in the secondary pack label include:
Brand name: Amlovie 10

Composition: Amlodipine Besylate equivalent to Amlodipine 10 mg

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)

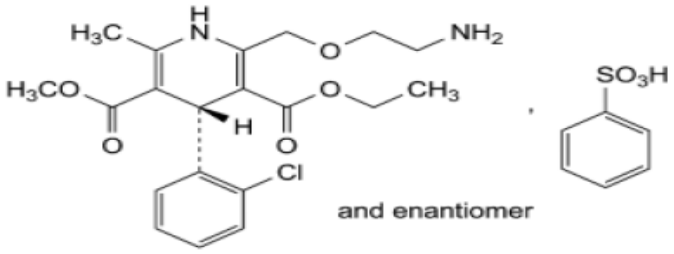
Information on quality of the API was submitted in form of CEP

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

Molecular formula: C26H31ClN2O8S

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 10 is a white to almost white tablets of oblong shape with a score on one side of the tablets. Amlovie 10 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.

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 10 was established through bioequivalence trial reference BLCL-AML-EU-01 (EudraCT 2016-002850-19)

Study title	A single-dose, open-Label, randomized, two-sequence, two-treatment, two-period crossover bioequivalence study of Amlodipine 10 mg tablets manufactured by Bluepharma – Industria Farmaceutica, S.A., Portugal, and Pfizer's reference product Norvasc® (Amlodipine) 10 mg tablets in healthy subjects under fasting conditions
Study design	Open-Label, Randomized, Two-Sequence, Two-Treatment, Two-Period Crossover Study
Study site	
Study dates	2nd November, 2016 to 22nd December, 2016
Primary objective	To assess the in vivo response of the dosage form with respect to extent of and rate of absorption of Amlodipine 10 mg tablets manufactured of Bluepharma – Industria Farmaceutica, S.A., Portugal, and Pfizer's reference product Norvasc® (Amlodipine) 10 mg tablets in healthy subjects under fasting conditions
Secondary objective	To monitor the safety and tolerability of a single dose of Amlodipine tablets administered in healthy human adults
Number of participants	25
Monitored parameters	Tmax, Cmax, AUC0→t, T1/2

Investigational medicinal products	Test Product	Reference product
	Strength: 10 mg Batch number: L151340 Expiry date: 31/12/2018	Strength: 10 mg Batch number: 00000624 Expiry date: 11/2019
Analytical method	HPLC/MS/MS	
Statistical method	SAS® 9.3 - ANOVA	

Efficacy results are summarized as follows: (n=25)

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.hr/mL)	246.165	247.340	99.52	96.36 – 102.79	23	6.7
AUC0-inf (units)	-	-	-	-	-	
Cmax (ng/mL)	8.290	8.397	98.72	93.68 – 104.04	23	10.8

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, Amlovie 10 (Amlodipine 10 mg) tablets is equivalent and interchangeable with Norvasc® (Amlodipine) 10 mg tablets 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. Amlovie 10 (Amlodipine 10 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