1.3.1 Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name : **AMLODIPINE TABLETS BP 10 mg**
1.2 Generic Name : **AMLODIPINE TABLETS BP 10 mg**
1.3 Strength : 10 mg/Tablets
1.4 Pharmaceutical Form : Uncoated Tablets
1.5 Packaging : 14 Tablets are packed in Alu-pvc Blister and such 2 Blister are packed in monocarton along with pack insert

2. QUALITY AND QUANTITATIVE COMPOSITION

Batch size: 4.71 Lac.

Sr. No.	Ingredients	Specification	Qty/ Tablets (mg)	Function
	DRY MIXING			
1.	Amlodipine Besylate Eq. to Amlodipine	BP	10.00	Active
2.	M.C.C. PH-102	BP	10.00	Filler
3.	Lactose	BP	8.00	Lubricant
4.	D.C.P.	BP	37.00	Binder
5.	Maize Starch	BP	22.36	Binder
	BINDER			
6.	Maize Starch	BP	3.00	Binder
7.	Methyl paraben	BP	0.20	Preservative
8.	Propyl paraben	BP	0.30	Preservative
9.	Purified water	BP	Q.S.	Vehicle
	BLENDING/ LUBRICATION			
10.	Talcum powder	BP	2.00	Binder
11.	Mag. Stearate	BP	2.00	Binder
12.	Sod. Starch glycolate	BP	5.20	Super Disintegrant
	Total weight of Tablets		**100.00 mg**	

***Calculation:**

Molecular weight of Amlodipine Besylate ($C_{26}H_{31}ClN_2O_8S$,) is 567.05 g/mol

Molecular weight of Amlodipine ($C_{20}H_{25}ClN_2O_5$) is 408.879 g/mol

$$\text{Sterile Amlodipine Besylate} = \frac{\text{Molecular weight of Amlodipine Besylate}}{\text{Molecular weight of Amlodipine}} \times \text{Lable claim}$$

$$= \frac{567.05}{408.879} \times 10$$

$$= 13.86 \text{ mg}$$

Therefore,

Amlodipine Besylate equivalent to Amlodipine on 100% assay base

Therefore, 13.86 mg of Amlodipine Besylate equivalent to Amlodipine 10 mg

3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Off white coloured tablet plain on each side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Hypertension

Chronic stable angina pectoris

Vasospastic (Prinzmetal's) angina

4.2 Posology and method of administration

Posology

Adults

For both hypertension and angina the usual initial dose is 10 mg amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.

Renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing ranges. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with

severe hepatic impairment. Paediatric population Children and adolescents with hypertension from 6 years to 17 years of age

The recommended antihypertensive oral dose in paediatric patients aged 6-17 years is 5 mg once daily as a starting dose, up-titrated to 10 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 10 mg daily have not been studied in paediatric patients Doses of amlodipine 2.5 mg are not possible with this medicinal product.

Children under 6 years old

No data are available.

Method of administration

Tablet for oral administration.

4.3 Contraindications

Amlodipine is contra-indicated in patients with:

- Severe hypotension
- shock (including cardiogenic shock)
- hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients.
- haemodynamically unstable heart failure after acute myocardial infarction
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

Patients with cardiac failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment

Use in elderly patients

In the elderly, increase of the dosage should take place with care.

Use in renal failure

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

4.6 Pregnancy and lactation

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding it is not known whether amlodipine is excreted in breast milk.

A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the woman.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (≥1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety),

		depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, rhinitis
	Very rare	Cough
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia

Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema
	Very rare	Angiodema, erythema, multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	Common	Ankle swelling
	Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynecomastia
General disorders and administration site conditions	Common	Oedema, fatigue
	Uncommon	Chest pain, asthenia, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

4.9 Overdose

In humans, experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdoses could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects.

ATC code: C08CA01

Mode of action

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.

The mechanism of action also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes and gout.

Use in patients with coronary artery disease (CAD)

5.2 Pharmacokinetic properties

Absorption, distribution, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in urine.

Use in hepatic impairment:

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

5.3 Preclinical safety data

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C. Store in the original package..

6.5 NATURE AND CONTENTS OF CONTAINER

14 Tablets are packed in an Alu-pvc blister and such 2 blister is packed in a printed monocarton along with pack insert.

7. MANUFACTURER

WINTECH PHARMACEUTICAL

Office No. 2& 3, 3rd floor , Broadway shopping

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Tel : (+ 9122) 42123456 (100 lines)

Fax : 42123400

8. DISTRIBUTED BY:

EXXON PHARMA NIGERIA LTD

Address: Arcee textile mill compound, Aswani road,

Block A, Plot 2B, oshodi Industrial scheme,

Isolo, Lagos Nigeria.

9. DATE OF REVISION OF THE TEXT

April, 2021

10. DOSIMETRY (IF APPLICABLE)

Not Applicable