1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Jawa Amlodipine (Amlodipine Tablets 5 mg)

1.1 Strength

Each uncoated tablet contains:
Amlodipine Besilate BP
Eq. to Amlodipine : 5 mg
Excipients : Q.S.

1.2 Pharmaceutical form

Uncoated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Description: Yellow coloured capsule shape biconvex uncoated tablet with breakline on one side.

Sr. No.	Name of raw material	Specification	Label Claim (mg)	Qty. per Tablets (mg)
1.	Amlodipine Besilate Eq. to Amlodipine	BP	6.93 ≅ 5.00	6.93 ≅ 5.00
2.	Maize Starch	BP	-	74.57
3.	Lake Quinoline Yellow Colour	In-House	-	0.50
4.	Lactose	BP	-	65.000
5.	Povidone	BP	-	5.000
6.	Isopropyl alcohol*	BP	-	Q.S
7.	Purified talc	BP	-	2.000
8.	Magnesium stearate	BP	-	3.000
9.	Sodium starch Glycolate	BP	-	3.000

* Removed after drying and does not present in the finished product

BP : British Pharmacopoeia

3. PHARMACEUTICAL FORM

Uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.
Chronic stable and vasospastic angina pectoris.

4.2 Posology and method of administration

For oral use.
The tablets should be taken with a glass of liquid (e.g. a glass of water) independently from meals.
Simultaneous intake of grapefruit or grapefruit juice has no influence on the effect of amlodipine.
Adults:
For the treatment of hypertension and angina pectoris, the usual dose is 5 mg amlodipine once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, the dose can be increased to a maximum dose of 10 mg daily (given as a single dose) depending on the individual response of the patient. Amlodipine can be used as monotherapy or in combination with anti-anginal medication in patients suffering from angina pectoris.
Children with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients. The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.
Elderly patients:
For elderly patients, the normal dose is recommended; however, caution is advised when the dose is increase.
Patients with renal impairment:
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 dialyzable.
Patients with hepatic impairment:
In patients with hepatic impairment, no dosage regimen has been defined, therefore amlodipine should be administered with caution.

4.3 Method of administration

Route of administration is oral.

4.4 Contraindications

Amlodipine is contraindicated in patients with:
- hypersensitivity to dihydropyridine derivatives, amlodipine or or any of the excipients
- severe hypotension

- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction.

4.5 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 heart 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 dialyzable

4.6 Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

4.7 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 hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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.

4.8 Additional information on special populations

Not Applicable

4.9 Paediatric population

Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients.
Children under 6 years old
No data are available.

4.10 Fertility, 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 (see section 5.3).

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.

Breastfeeding
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 mother.

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

4.11 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.

4.12 Undesirable effects

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.
Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Musculoskeletal System: arthralgia, arthrosis, muscle cramps, myalgia.
Psychiatric: sexual dysfunction (male1 and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: dyspnea, epistaxis.
Skin and Appendages: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.
Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System: micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, sweating increased.
Metabolic and Nutritional: hyperglycemia, thirst.
Hemopoietic: leukopenia, purpura, thrombocytopenia.

4.13 Overdose

Available data suggest that gross overdosage 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.
Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption.
In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. 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. 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 – Dihydropyridine derivatives.
ATC code: C08CA01.
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 of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation 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.
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

5.2 Pharmacokinetic properties

A 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.
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 the urine.

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 besilate 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.
Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch	BP
Lake Quinoline Yellow Colour	IHS
Lactose	BP
Povidone	BP
Isopropyl alcohol	BP
Purified talc	BP
Magnesium stearate	BP
Sodium starch Glycolate	BP

6.2 Icompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dark, dry place, Not exceeding 30^0C temp.

6.5 Nature and contents of container

Pack Style: 10 x 1 0 Alu-PVC Pack

6.6 Special precautions for disposal and other handling

Store in dark, dry place, not exceeding 30ºC temp.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

MARKETING AUTHORISATION HOLDER
Jawa International Limited
Jawa House Compound, Plot 6,
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8. MARKETING AUTHORISATION NUMBER

A4-2614

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

11th September 2014

10. DATE OF REVISION OF THE TEXT

Mar 2020