SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Product Name **:** Amlibon 5 (Amlodipine Besylate Tablets 5 mg)

Strength **:** 5 mg

Pharmaceutical Form **:** White to off white, capsule shaped, biconvex, uncoated tablets, debossed, "ML22" on one side and plain on the other side.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated contains:

Amlodipine Besylate USP

Equivalent to Amlodipine …….. 5mg

<For the full list of excipients, see section 6.1.>

Ingredient	**Reference to quality standard**	**Weight in mg/tablets**
Dry mixing & Prelubrication		
Amlodipine Besylate*	USP	6.935
Microcrystalline Cellulose (Avicel PH 101)	USP/NF	30.00
Dibasic calcium phosphate, Anhydrous (Calipharm A)	USP/NF	33.00
Sodium starch glycolate (Type A)	USP/NF	6.00
Dibasic calcium phosphate, Anhydrous (A-Tab)	USP/NF	30.00
Microcrystalline cellulose$ (Avicel PH 102)	USP-NF/Ph. Eur	92.065
Lubrication		
Magnesium Stearate	USP/NF	2.00
Total weight of Tablets		200

USP/NF--United state Pharmacopoeia/ National formulary
*6.935 of Amlodipine Besylate is equivalent to 5mg of Amlodipine

Calculations:
The quantity mentioned for Amlodipine Besylate is based on 100% assay on anhydrous basis as Amlodipine Besylate and 0 % water (by KF). Based on actual assay and water content of Amlodipine Besylate calculate the quantity as per following formula:

mg/tablet = 5 x 567.1# x 100 x 100
408.88 Assay on anhydrous basis as Amlodipine Besylate 100 - water (by KF)
$ The quantity of microcrystalline cellulose (Avicel PH 102) to be adjusted to keep the final tablet
weight 200mg for Amlodipine Besylate tablets 5mg
Molecular weight of Amlodipine Besylate and Amlodipine are 567.1 and 408.88 respectively.

3. PHARMACEUTICAL FORM

Amlibon 5 mg tablets

White to off white, capsule shaped, biconvex, uncoated tablets, debossed, "ML22" on one side and plain on the other 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 5 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 anti-anginal 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

Patients with 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 range.

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.

Patients with 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.

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 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.

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 amlodipine, dihydropyridine derivatives or any of the excipients .

• haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days)

• 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.

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, but this was not indicating an aggravation of the heart failure.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.

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.

Elderly patients

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

Renal failure

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

Amlodipine is not dialyzable.

Paediatric population (under 18 years of age)

Amlodipine should not be given to children due to insufficient clinical experience

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 resulting in an increased risk of hypotension. 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:

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum).

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.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates.
Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors,
amlodipine may increase exposure of mTOR inhibitors.

Ciclosporin

No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporin were observed.

Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.

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 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 .

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

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. 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.

4.7 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

The following undesirable effects 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	≥1/10000 to ≤1/1000
Very Rare	≤ 1/ 10000
Not known	Frequency cannot be established from available data

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

System Organ Class	Frequency	Undesirable effects
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, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis

Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepato-biliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic Epidermal Necrolysis
Musculoskeletal, connective tissue and bone disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

4.9 Overdose

In humans experience with intentional overdose is limited.

Symptoms:

Available data suggest that gross overdose 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.

Management:
Clinically significant hypotension due to amlodipine overdose 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 10 mg 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

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:

1. 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.
2. 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).

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absorption of amlodipine is not influenced by concomitant food intake. Absolute bioavailability of the unchanged active substance is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours after administration

Distribution

The volume of distribution is approximately 21 l/kg. The pKa of amlodipine is 8.6. In vitro studies have shown that amlodipine is bound to plasmatic proteins up to 97.5%.

Biotransformation

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elimination

The plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. 60% of metabolites are excreted in the urine.

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%.

Elderly

Increase in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

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/m^2 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.

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/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no medicinal product related effects at either the gene or chromosome levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Avicel PH 101 & 102), Dibasic calcium phosphate, Anhydrous (Calipharm A), Sodium starch glycolate (Type A), Dibasic calcium phosphate, Anhydrous (A-Tab), Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do note store above 30 ° C protect from light

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

HDPE container pack of 90 tablets packed in a carton along with pack insert.

6.6 Special precautions for disposal <and other handling>

No special requirements

7. MARKETING AUTHORISATION HOLDER

MEGA LIFESCIENCES Public Company Limited.

384, Soi 6, Pattana 3 Road, Bangpoo Industrial Estate,

Moo 4, Praeksa, Muang Samutprakarn,

Samutprakarn 10280, Thailand

Manufacturing Site address:

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Daman (UT)- 396 210, India

Phone No.: +91-260-2240125

8. MARKETING AUTHORISATION NUMBER(S) – 09032/09130/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/10/2023

10. DATE OF REVISION OF THE TEXT

17th January 2024

11. Reference

Not Applicable