SUMMARY OF PRODUCT CHARACTERISTICS

1-Name of the Medicinal Product:

1.1 Product Name

Derox-5 Tablet

1.2 Strength

Amlodipine Besilate 5 mg

1.3 Pharmaceutical Dosage Form

Tablet

2-Quality and Quantitative Composition:

ACTIVE INGREDIENTS	PER TABLET (MG)
Amlodipine Besilate	5 mg

For excipients, see 6.1

3-Pharmaceutical Form:

Oblong, white to off white uncoated tablet, bevel edged, shallow convex with break bar on one face and "HOVID" embossed on another face.

4-Clinical Particulars

4.1 Therapeutic indications

For the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoceptor blocking gent, or an angiotensin-converting enzyme inhibitor. Amlodipine is indicated for the first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/ vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine may be used where the clinical presentation suggests a possible vasospastic/ vasoconstrictive component but where vasospasm/ vasoconstriction has not been confirmed. Amlodipine may be used alone, as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

Posology and method of administration

Oral

For both hypertension and angina the usual initial dose is 5mg amlodipine once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

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

Use in the Elderly

A normal dose regiment is recommended. Amlodipine used at similar doses in elderly or younger patients, is equally well tolerated.

Use in Children
Safety and effectiveness of amlodipine in children have not been established.

Use in patients with Impaired Hepatic Function
As with all calcium antagonist, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

4.2 Contraindications

- Amlodipine is contraindicated in patients with known hypersensitivity to dihydropyridine derivatives.

4.4 Special warning and precautions for use

- General
    - Vasodilation induced by amlodipine is gradual in onset. Even though, acute hypotension has rarely been reported after oral administration of amlodipine, caution should be exercised when administering amlodipine particularly in patients with severe aortic stenosis. In general, calcium channel blockers should be used with caution in patients with heart failure.

- Beta-Blocker Withdrawal
    - Any withdrawal of beta-blocker should be by gradual reduction of the dose. Amlodipine is not a beta-blocker and thus gives no protection against the dangers of abrupt beta-blocker withdrawal.

- Patients with Hepatic Failure
    - Amlodipine should be administered with caution to patients with severe hepatic impairment. Amlodipine is extensively metabolised by the liver and the plasms elimination half-life (t½) is 56 hours in patients with impaired hepatic function. Amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

- Increased Angina and/or Myocardial Infarction
    - Rarely, increased frequency, duration and/or severity of angina or acute myocardial infarction have been documented in patients, particularly those with severe obstructive coronary artery disease, when started on calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been defined.

4.5 Interaction with other medicinal products and other forms of interactions
Antacids, Sucralfate, Metal Cations

- In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).
- Cimetidine
    - Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
- Sildenafil
    - A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When

amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

- Atorvastatin
    - Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
- Digoxin
    - Co-administration of amlodipine with digoxin did not change serum digoxin levels of digoxin renal clearance in normal volunteers.
- Ethanol (alcohol)
    - Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.
- Warfarin
    - Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazine diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

4.6 Pregnancy and lactation

Pregnancy

Studies have not been done in humans. No evidence of teratogenicity or other embryo/fetal toxicity was found in animal studies. Nevertheless, amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

4.7 Effects on ability to drive and use machine

NOT APPLICABLE

4.8 Undesirable effects

Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina.

The most commonly observed side effects were:

- Autonomic Nervous System
    - flushing
- Body as a Whole
    - fatigue
- Cardiovascular, General
    - edema
- Central & Peripheral Nervous System
    - dizziness, headache
- Gastrointestinal
    - abdominal pain, nausea

- Heart Rate/Rhythm
    - palpitations
- Psychiatric
    - somnolence

In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience include:
- Autonomic Nervous
    - dry mouth, increased sweating
- Body As A Whole
    - asthenia, back pain, malaise, pain, weight increase/decrease
- Cardiovascular, General
    - hypotension, syncope
- Central & Peripheral Nervous System
    - hypertonia, hypoesthesia/paresthesia, peripheral neuropathy, tremor
- Endocrine
    - gynecomastia
- Gastrointestinal
    - altered bowel habits, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
- Metabolic/ Nutritional
    - hyperglycemia
- Musculoskeletal
    - arthralgia, muscle cramps, myalgia
- Platelet/ Bleeding/ Clotting
    - purpura, thrombocytopenia
- Psychiatric
    - impotence, insomnia, mood changes
- Respiratory
    - coughing, dyspnea, rhinitis
- Skin/ Appendages
    - alopecia, skin discolouration, urticaria
- Special senses
    - taste perversion, tinnitus
- Urinary
    - increased urinary frequency, micturition disorder nocturia
- Vascular (Extracardiac)
    - vasculitis
- Vision
    - visual disturbances
- White Blood Cell/ R.E.S.
    - leucopenia

4.9 Overdose

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

Administration of activated charcoal to healthy volunteers immediately after or up to two hours of amlodipine 10 mg ingestion has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases.

Clinically significant hypotension due to overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremes, 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

Amlodipine is a dihydropyridine calcium antagonist. It acts by selective inhibition of transmembrane influx of calcium ions into the cardiac muscle and vascular smooth muscle through specific ion channels; thus modulating the contractile process of these cells. Amlodipine has a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Amlodipine exhibits negative inotropic effects in vivo, but appears to have no significant effect on the sinoatrial or atrioventricular node in humans.

Although not fully defined, the mechanisms of action of amlodipine in relieving angina is thought to be as follows:

Exertional Angina
Amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product. Therefore, in patients with exertional angina, myocardial oxygen demand is reduced, at any given level of exercise.

Vasospastic Angina
Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin and thromboxane A_2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

5.2 Pharmacokinetic properties

Absorption

Amlodipine is absorbed slowly and almost completely from the gastrointestinal tract. The absorption of amlodipine is not altered by the presence of food. Bioavailability has been estimated to be between 64 and 90%.

Distribution

Plasma concentrations peak between 6 and 12 hours post-dose. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in

hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Metabolisms:
About 90% of amlodipine is converted into inactive metabolites via hepatic metabolism.

Elimination:
10% of the parent compound and 60% of the metabolites are excreted in the urine.

Renal Impairment:
The pharmacokinetics of amlodipine is not significantly altered by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency may have decreased clearance of amlodipine and resulting increase in AUC of approximately 40-60%; a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

6-Pharmaceutical Particulars:

6.1 List of excipients

a) Microcrystalline cellulose M200D+
b) Microcrystalline cellulose PH102
c) Sodium Starch Glycolate
d) Magnesium Stearate

6.2 Incompatibilities

NOT APPLICABLE

6.3 Shelf life

3 years from date of manufacture

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Immediate Container/Packaging

Primary Packaging

1	Material description	:	Aluminium foil with high slip primer on bright surface and heat seal on matt surface/ Aluminium foil with high slip primer on bright surface and heat seal on matt surface
	Appearance	:	Bright surface/Matt surface each side
2	Material description	:	Push-through blister pack, consists of a clear thermoformable plastic (PVC) material and a heat-sealed, lacquered backing material.
	Appearance	:	White opaque
	Shrinkage	:	Not more than 8.0%

Outer Container / Secondary Packaging
Type: Unit box, Package Insert & Plain Carton for Derox 5 mg Tablet.

6.6 Special precautions for disposal
NOT APPLICABLE

7-Registrant

Marketing Authorization Holder:

Name	:	HOVID Bhd.
Address	:	121, Jalan Tunku Abdul Rahman, (Jalan Kuala Kangsar) 30010 Ipoh, Perak, Malaysia
Production Site	:	HOVID BHD., Lot 56442, 7 ½ miles, Jalan Ipoh/Chemor, 31200 Chemor, Perak, Malaysia.

8-Date of revision of the text :
February 2020

9-Dosimetry (If applicable) :
Not Applicable

10-Instruction for preparation of Radiopharmaceuticals (If applicable):
Not Applicable