

## Data Sheet

# CALVASC

***Amlodipine 5 mg tablets and 10 mg tablets***

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## Name of the Medicine

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CALVASC

Amlodipine 5 mg tablets and 10 mg tablets

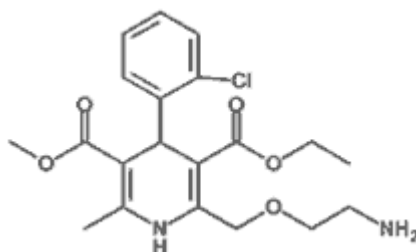
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## Description

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Amlodipine mesilate is a dihydropyridine derivative, and has the following chemical name: (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxy carbonyl-5-methoxy carbonyl-6-methyl-1,4-dihydropyridine mesilate. Amlodipine mesilate is slightly soluble in water and sparingly soluble in ethanol, and has a molecular weight of 504.98 (free base 408.9). The CAS number is 88150-42-9.

The structural formula is:



The tablets contain as excipients: microcrystalline cellulose; anhydrous calcium hydrogen phosphate; sodium starch glycolate and magnesium stearate.

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## Pharmacology

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### ***Mechanism of Action***

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and 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) and blunts smoking induced coronary vasoconstriction.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout a 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 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

### **Pharmacokinetics**

Amlodipine is not dialysable.

#### **Absorption**

Amlodipine is well absorbed orally with peak blood levels occurring 6-12 hours postdose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64 % (range 52-88 %). The absorption of amlodipine is unaffected by consumption of food.

#### **Distribution**

The volume of distribution is approximately 20 L/kg. *In vitro* studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

#### **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.

## ***Special Populations***

### **Use in Patients with Heart Failure**

Haemodynamic studies and exercise based controlled clinical trial 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

A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA Class III-IV heart failure receiving digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis and diuretics, amlodipine has no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo **(see Precautions)**.

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.

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## **Indications**

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CALVASC is indicated 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 CALVASC, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

CALVASC is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature.

CALVASC may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. CALVASC may be used alone as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or beta blockers.

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## Contraindications

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CALVASC tablets are contraindicated in patients with a known sensitivity to amlodipine, dihydropyridines or any of the inactive ingredients.

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## Precautions

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### ***General***

In a long term placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (**see Special Populations**).

### ***Use in Pregnancy and lactation***

Safety of CALVASC in human pregnancy or lactation has not been established. Amlodipine did not demonstrate any foetotoxic or teratogenic potential in animal reproductive studies other than to delay parturition and prolong labour in rats at a dose level fifty times the maximum recommended dose in humans. No mutagenic activity has been found in tests for gene mutations or cytogenic assays. Accordingly, use in pregnancy is recommended only when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

### ***Use in Children***

Safety and effectiveness of CALVASC in children have not been established.

### ***Other Precautions***

As with all calcium channel blockers, CALVASC half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The compound should therefore be administered with caution in these patients.

### ***Effects on ability to drive or Operate Machinery***

Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive.

### ***Interactions***

Amlodipine has been safely administered with thiazide diuretics, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, long-

acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory agents, antibiotics, and oral hypoglycaemic agents.

*In vitro* data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

### **Special Studies: Effect of other agents on amlodipine**

*Cimetidine*: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

*Grapefruit Juice*: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Aluminium/Magnesium (antacid)*: Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on 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.

### **Special Studies: Effect of amlodipine on other agents**

*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 or digoxin renal clearance in healthy volunteers.

*Ethanol (alcohol)*: Single and multiple 10mg 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.

*Cyclosporin*: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

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## **Adverse effects**

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### **Common**

CALVASC is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were headache, oedema, fatigue, somnolence, nausea, abdominal pain, flushing, palpitations and dizziness. In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine have been observed.

### **Less Common**

Less commonly observed side effects in marketing experience include alopecia, skin discolouration, altered bowel habits, arthralgia, asthenia, back pain, dyspepsia (including gastritis), vomiting, coughing, dyspnoea, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, leucopenia, malaise, pain, weight increase/decrease, insomnia, mood changes, dry mouth, taste perversion, tinnitus, muscle cramps, myalgia, hypertonia, hypoesthesia/paresthesia, peripheral neuropathy, tremor, pancreatitis, increased sweating, hypotension, syncope, purpura, thrombocytopenia, vasculitis and visual disturbances. In many instances, causal association is uncertain.

Rarely, allergic reactions including pruritis, rash, angioedema and erythema multiforme have been reported.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

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## **Dosage and Administration**

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

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

The time to reach peak plasma concentrations of CALVASC is similar in elderly and younger subjects. CALVASC clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. CALVASC, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

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

CALVASC is extensively metabolised to inactive metabolites with 10 % excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. CALVASC may be used in such patients at normal doses.

CALVASC is not recommended for use in children.

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## Overdosage

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### *Symptoms*

In humans, experience with intentional overdosage is limited. Available data suggest that gross overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

### *Management*

Gastric lavage may be worthwhile in some cases as peak blood levels do not occur for 6-12 hours. 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. Dialysis is not likely to be of benefit since amlodipine is highly protein-bound.

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## Presentation and Storage conditions

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**CALVASC 5 mg tablets:** white to off white, round, biconvex tablets; 8 mm in diameter, embossed with "5" on one side, each containing amlodipine mesilate equivalent to 5 mg amlodipine.

**CALVASC 10 mg tablets:** white to off white, round, biconvex tablets; 10.5 mm in diameter, scored on one side, embossed with "10" on the other side, each containing amlodipine mesilate equivalent to 10 mg amlodipine.

### *Storage*

Store below 25 °C. Shelf life 3 years. Protect from light and moisture.

### *Pack quantities*

**CALVASC 5 mg:** Blister pack of 30 tablets, sample pack of 15 tablets.

**CALVASC 10 mg:** Blister pack of 30 tablets.

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## **Medicine Classification**

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Prescription medicine

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## **Name and Address of Sponsor**

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## **Date of Preparation**

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November 2006.