

DATA SHEET

NORVASC[®]

amlodipine besylate
5 mg and 10 mg tablets

PRESENTATION

NORVASC 5 mg tablets are white emerald shaped scored tablets, marked with NVC/5 on one side and Pfizer on the other, each containing amlodipine besylate equivalent to 5 mg amlodipine.

NORVASC 10 mg tablets are white emerald shaped scored tablets, marked with NVC/10 on one side and Pfizer on the other, each containing amlodipine besylate equivalent to 10 mg amlodipine.

In addition to amlodipine besylate, each NORVASC tablet contains the following inactive ingredients: microcrystalline cellulose; dibasic calcium phosphate (anhydrous); sodium starch glycollate; magnesium stearate.

INDICATIONS

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

NORVASC 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. NORVASC may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. NORVASC 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.

DOSAGE AND ADMINISTRATION

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

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

Use in the Elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

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

NORVASC, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Use in Renal Disease

Amlodipine 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. NORVASC may be used in such patients at normal doses. Amlodipine is not dialysable.

Use in Children

NORVASC is not recommended for use in children.

CONTRAINDICATIONS

NORVASC is contraindicated in patients with a known sensitivity to amlodipine, dihydropyridines or any of the inactive ingredients.

WARNINGS AND PRECAUTIONS

Use in Patients with Heart Failure

In a long term placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic etiology, 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 **FURTHER INFORMATION, Use in Patients with Heart Failure**).

Pregnancy and Lactation

Category C.

Safety of amlodipine 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 Patients with Impaired Hepatic Function

As with all calcium channel blockers, amlodipine 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.

Paediatric Use

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

Effects on Ability to Drive and Use Machinery

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

ADVERSE EFFECTS

NORVASC is well-tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed adverse 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 has been observed.

Less commonly observed adverse effects in marketing experience include:

MedDRA System Organ Class	Undesirable Effects
<i>Blood and Lymphatic System Disorders</i>	Leucopenia, thrombocytopenia
<i>Metabolism and Nutrition Disorders</i>	Hyperglycaemia
<i>Psychiatric Disorders</i>	Insomnia, mood changes
<i>Nervous System Disorders</i>	Hypertonia, hypoesthesia/paresthesia, peripheral neuropathy, syncope, taste perversion, tremor
<i>Eye Disorders</i>	Visual disturbances
<i>Ear and Labyrinth Disorders</i>	Tinnitus
<i>Vascular Disorders</i>	Hypotension, vasculitis
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	Cough, dyspnoea, rhinitis
<i>Gastrointestinal Disorders</i>	Altered bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
<i>Skin and Subcutaneous Tissue Disorders</i>	Alopecia, increased sweating, purpura, skin discolouration, urticaria
<i>Musculoskeletal and Connective Tissue</i>	Arthralgia, back pain, muscle cramps,

<i>Disorders</i>	myalgia
<i>Renal and Urinary Disorders</i>	Increased urinary frequency, micturition disorder, nocturia
<i>Reproductive System and Breast Disorders</i>	Gynaecomastia, impotence
<i>General Disorders and Administration Site Conditions</i>	Asthenia, malaise, pain
<i>Investigations</i>	Weight increase/decrease

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 hospitalisation 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.

INTERACTIONS

NORVASC 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).

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 to 20 mg daily in patients on amlodipine.

Grapefruit Juice: 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.

CYP3A4 Inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients, the plasma concentration of amlodipine was increased. The clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 Inducers: There are no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum* (St John's Wort)) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Special Studies: Effect of Other Agents on Amlodipine

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

Cyclosporin: No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. Various studies in renal transplant patients report that amlodipine co-administration with cyclosporin affect trough concentrations of cyclosporin from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

OVERDOSAGE

Available data suggest that overdosage might be expected to cause excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonist. Hypotension and bradycardia are usually seen within 1 to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalised; another (120 mg) was hospitalised, underwent gastric lavage and remained normotensive; a third one (105 mg) was hospitalised and had hypotension (90/50 mmHg) which normalised following plasma expansion. Death resulted from a mixed overdose of 140 mg and 10 mefenamic acid capsules in a 15-year old girl, and from a mixed overdose of amlodipine 70 mg and an unknown quantity of oxazepam in a 63-year old woman. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg NORVASC (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of NORVASC 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. 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.

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

FURTHER INFORMATION

Actions

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 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) 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 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 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

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 of 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 had 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 **WARNINGS AND 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.

Pharmacokinetics

Absorption

Amlodipine is well absorbed orally with peak blood levels occurring 6-12 hours post-dose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64% (range 52-88%). The volume of distribution is approximately 20 L/kg. The absorption of amlodipine is unaffected by consumption of food. *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. Steady state plasma levels are reached after 7-8 days of consecutive 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.

Amlodipine is not dialysable.

Other

Amlodipine besylate is a dihydropyridine derivative, and has the following chemical name:

3-ethyl 5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzene sulphonate.

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol, and has a molecular weight of 567.1 (free base 408.9).

PHARMACEUTICAL PRECAUTIONS

Store below 25°C.

Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

5 mg x 30 tablets

10 mg x 30 tablets.

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