

AUSTRALIAN PRODUCT INFORMATION – BTC AMLODIPINE (AMLODIPINE)

1 NAME OF THE MEDICINE

Amlodipine besilate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg or 10 mg of amlodipine besilate, equivalent to 5 mg or 10 mg of Amlodipine.

For the full list of excipients see section **6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

BTC Amlodipine 5 mg Tablet:

White to off white, round, biconvex, uncoated tablets with 'E21' embossing on one side and breakline on other side.

BTC Amlodipine 10 mg Tablet:

White to off white, round, biconvex, uncoated tablets with '10' embossing on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

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

Angina

- Amlodipine is indicated for the first line treatment of chronic stable angina. amlodipine may be used alone, as monotherapy or in combination with other antianginal drugs.>

4.2 DOSE AND METHOD OF ADMINISTRATION

For hypertension or angina the usual initial dose is 2.5 to 5 mg once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

Small, fragile or elderly individuals, or patients with hepatic insufficiency should be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. See section **4.8 Adverse effects (undesirable effects)** for information related to dosage and side effects.

Co-Administration with Other Antihypertensive and/or Antianginal Drugs

Amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

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

4.3 CONTRAINDICATIONS

Amlodipine is contraindicated in patients with a known hypersensitivity to amlodipine, other dihydropyridines, or any of the inactive ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Increased Angina

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

Amlodipine should be used with caution in the presence of a fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Peripheral Oedema

Mild to moderate peripheral oedema was the most common adverse event in the clinical trials (see section **4.8 Adverse effects (undesirable effects)**). The incidence of peripheral oedema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

Use in hepatic impairment

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see section **4.2 Dose and method of administration**).

Use in renal impairment

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 the degree of renal impairment. Amlodipine may be used at normal doses in patients with renal failure.

Amlodipine is not dialysable.

Use in the elderly

In elderly patients (≥ 65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials, the incidence of adverse events in elderly patients was approximately 6% higher than that of younger population (< 65 years). Adverse events include oedema, muscle cramps and dizziness. Amlodipine should be used cautiously in elderly patients.

Paediatric use

Safety and effectiveness have not been established in children.

Effects on laboratory tests

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine or liver function tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Special studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

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 amlodipine and simvastatin resulted in an increase in exposure to simvastatin compared to simvastatin alone. The Product Information for simvastatin should be reviewed for the appropriate dose of simvastatin when the patient is prescribed amlodipine concurrently.

Grapefruit Juice

Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. 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 when administered with CYP3A4 inhibitors.

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin

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 decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

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 16 patients 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.

Ethanol (Alcohol)

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

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 co-administration of amlodipine with cyclosporin affects the trough concentrations of cyclosporin, and consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See section 5.3 **Preclinical safety data, Effects on fertility.**

Use in pregnancy

Category C

Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly, they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

The safety of amlodipine in human pregnancy or lactation has not been established.

Use in lactation

It is not known whether amlodipine is excreted in human milk. In the absence of this information, breast-feeding should be discontinued during treatment with amlodipine.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Amlodipine has been evaluated for safety in more than 11000 patients in clinical trials worldwide.

In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse events reported during therapy with amlodipine were of mild or moderate severity.

In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse events was required in only about 1.5% of patients and was not significantly different from placebo (about 1%).

The most common side effects are headache and oedema. The incidence (%) of side effects which occurred in a dose-related manner are in Table 1.

Table 1: Incidence (%) of side effects which occurred in a dose-related manner

| | 2.5 mg | 5.0 mg | 10.0 mg | Placebo |
|----------------------|---------------|---------------|----------------|----------------|
| Adverse Event | N = 275 | N = 296 | N = 268 | N = 520 |
| Oedema | 1.8 | 3.0 | 10.8 | 0.6 |
| Dizziness | 1.1 | 3.4 | 3.4 | 1.5 |
| Flushing | 0.7 | 1.4 | 2.6 | 0.0 |
| Palpitation | 0.7 | 1.4 | 4.5 | 0.6 |

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials are in Table 2.

Table 2: Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials

| Adverse Event | Placebo Controlled Studies | |
|-----------------------|-----------------------------------|-----------------------------|
| | Amlodipine % (N = 1730) | Placebo % (N = 1250) |
| Headache | 7.3 | 7.8 |
| Fatigue | 4.5 | 2.8 |
| Nausea | 2.9 | 1.9 |
| Abdominal Pain | 1.6 | 0.3 |
| Somnolence | 1.4 | 0.6 |

The following events occurred in $\leq 1\%$ but $> 0.1\%$ of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Blood and Lymphatic System Disorders

Leucopenia, thrombocytopenia.

Cardiac Disorders

Tachycardia.

Ear and Labyrinth Disorders

Tinnitus, vertigo.

Eye Disorders

Abnormal vision, conjunctivitis, diplopia, eye pain.

Gastrointestinal Disorders

Altered bowel habits, constipation, diarrhoea, dry mouth, dyspepsia*, dysphagia, flatulence, gingival hyperplasia, pancreatitis, vomiting.

General Disorders and Administration Site Conditions

Asthenia*, malaise, pain, rigors, thirst.

Immune System Disorders

Allergic reactions.

Investigations

Weight gain.

Metabolism and Nutrition Disorders

Anorexia, hyperglycaemia.

Musculo-Skeletal and Connective Tissue Disorder

Arthralgia, arthrosis, back pain, muscle cramps*, myalgia.

Nervous System Disorders

Hypoesthesia, paresthesia, peripheral neuropathy, postural dizziness, syncope, tremor.

Psychiatric Disorders

Abnormal dreams, anxiety, depersonalisation, depression, insomnia, mood changes, nervousness.

Renal and Urinary Disorders

Micturition disorder, micturition frequency, nocturia

Reproductive System and Breast Disorders

Gynaecomastia, sexual dysfunction (male* and female).

Respiratory Thoracic and Mediastinal Disorders

Dyspnoea*, epistaxis.

Skin and Subcutaneous Tissue Disorders

Alopecia, angioedema, pruritus*, purpura, rash*, rash erythematous, rash maculopapular, sweating increased.

Vascular Disorders

Hot flushes, hypotension, peripheral ischaemia, postural hypotension, vasculitis.

*These events occurred in less than 1% of patients in placebo controlled trials, but the incidence of these adverse effects was between 1% and 2% in all multiple dose studies.

The following events occurred in 0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, erythema multiforme, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, xerophthalmia and weight decrease.

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.

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (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.

There have been post-marketing reports of extrapyramidal disorder in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus and abnormal lipid profiles.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems> and contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Symptoms

Available data suggest that overdose might be expected to cause excessive peripheral vasodilation 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 overdose 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 amlodipine (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.

Treatment

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. Intravenous calcium may help to reverse the effects of calcium entry blockade.

Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 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*.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 vascular smooth muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionised compound ($pK_a=8.6$), and its kinetic interaction with the calcium channel receptor is characterised by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

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. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the 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. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A₂ analogue both in normal and in ischaemic regions.

Haemodynamics

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreased arterial blood pressure and increased heart rate in haemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.

The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in

normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Clinical trials

Studies in Patients with Congestive Heart Failure

Amlodipine has been compared to placebo in four 8-12 weeks studies of patients with New York Heart Association (NYHA) class II/III heart failure, involving a total of 697 patients. Although efficacy in regard to the primary and secondary endpoints was not demonstrated, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo: the cardiac morbid events represented about 25% of the endpoints in the study.

In this study amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure compared to placebo.

Electrophysiologic Effects

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30 minute interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse events on electrocardiographic parameters were observed.

In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Effects in Hypertension

In patients with hypertension once daily dosing provides clinically significant reductions in blood pressure in both the supine and standing positions throughout the 24 hour interval post dose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24 hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to 1 year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

Effects in Chronic Stable Angina

In patients with angina, once daily administration of amlodipine increases total exercise time to angina onset and total work time to 1 mm ST segment depression and decreases both angina attack frequency and nitroglycerine tablet consumption. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Other

In clinical trials amlodipine has shown no harmful effect on lipid levels. Dihydropyridine calcium channel blockers have not been associated with any adverse metabolic effects and are suitable for use in patients with asthma, diabetes and gout.

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. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2-8 hours) in patients with hepatic insufficiency. Absolute bioavailability has been estimated to be between 64 and 90%.

Distribution

The bioavailability of amlodipine is not altered by the presence of food. 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.

Metabolism

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

Excretion

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.

Special Populations

Elderly (≥65 years)

In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Effects on fertility

In animal studies, amlodipine did not affect fertility in rats at oral doses up to 18 mg/kg (base).

Use in pregnancy

In animal studies, amlodipine had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg). Amlodipine (10 mg/kg as besilate salt, 7 mg/kg base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- microcrystalline cellulose
- calcium hydrogen phosphate dihydrate
- sodium starch glycollate type A
- colloidal anhydrous silica
- magnesium stearate.

6.2 INCOMPATIBILITIES

See section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

BTC Amlodipine 5 mg Tablet:

Blister pack (opaque PVDC coated PVC/ aluminium) of 10, 14, 30, 28, 50, 56, or 84 tablets.
AUST R: 307473

BTC Amlodipine 10 mg Tablet:

Blister pack (opaque PVDC coated PVC/ aluminium) of 10, 14, 30, 28, 50, 56, or 84 tablets.
AUST R: 307474

Not all strengths may be available

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

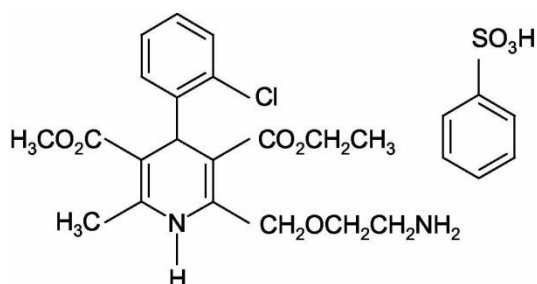
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Amlodipine besilate is a dihydropyridine derivative.

Amlodipine besilate is a white crystalline powder and is slightly soluble in water and sparingly soluble in ethanol.

Chemical structure



Chemical Name: 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.

Molecular Formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular Weight: 567.1 (free base 408.9).

CAS number

111470-99-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

IPCA PHARMA (AUSTRALIA) PTY LTD
6 Morotai Avenue
ASHBURTON
VIC 3147

DISTRIBUTOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

Tel: (02) 8877 8333

Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

25th October 2018

10 DATE OF REVISION

15th November 2018

Summary table of changes

| Section Changed | Summary of new information |
|-----------------|--|
| 6.5 | Inclusion of additional pack size of 10's, 30's and 50's tablets |
| | |
| | |