AMLODIPINE BESYLATE - amlodipine besylate tablet
Unit Dose Services

HIGHLIGHTS OF PRESCRIBING INFORMATION
Amlodipine besylate tablets These highlights do not include all the information needed to use Amlodipine Besylate safely and effectively. See full prescribing information for Amlodipine Besylate. Amlodipine Besylate (Amlodipine Besylate) TABLET for ORAL use. Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Amlodipine besylate, USP is a calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:

- Hypertension ( ) 1.1
- Coronary Artery Disease ( ) 1.2
- Chronic Stable Angina
- Vasospastic Angina (Prinzmetal's or Variant Angina)
- Angiographically Documented Coronary Artery
- Disease in patients without heart failure or an ejection fraction < 40%

DOSAGE AND ADMINISTRATION

- Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. ( ) 2.1
- Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily. ( ) 2.1
- Pediatric starting dose: 2.5 mg to 5 mg once daily. ( ) 2.2

Doses in excess of 5 mg daily have not been studied in pediatric patients. ( ) **Important Limitation:**2.2

DOSAGE FORMS AND STRENGTHS

2.5 mg, 5 mg, and 10 mg Tablets ( ) 3

CONTRAINDICATIONS

- Known sensitivity to amlodipine ( ) 4

WARNINGS AND PRECAUTIONS

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, because of the gradual onset of action, acute hypotension is unlikely. ( ) 5.1
- Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine besylate tablets, particularly in patients with severe obstructive coronary artery disease. ( ) 5.2
- Titrate slowly when administering calcium channel blockers to patients with severe hepatic impairment. ( ) 5.4

ADVERSE REACTIONS

Most common adverse reactions are headache and edema which occurred in a dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are headache, fatigue, nausea, abdominal pain, and somnolence. ( ) 6

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals at 1-866-495-8330 and or FDA at 1-800-FDA-1088 or www.camberpharma.com*www.fda.gov/medwatch.*

DRUG INTERACTIONS

- If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin. ( ) 7.7

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if the potential benefit justifies the potential risk. ( ) 8.1
- Nursing: Discontinue when administering amlodipine besylate tablets. ( ) 8.3
- Pediatric: Effect on patients less than 6 years old is not known. ( ) 8.4
- Geriatric: Start dosing at the low end of the dose range, due to the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. ( ) 8.5

Revised: 7/2012

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1. Hypertension

Amlodipine besylate tablets, USP are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

1.2. Coronary Artery Disease (CAD)

Chronic Stable Angina

Amlodipine besylate tablets, USP are indicated for the symptomatic treatment of chronic stable angina. Amlodipine besylate tablets, USP may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

Amlodipine besylate tablets, USP are indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine besylate tablets, USP may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD

In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, amlodipine besylate tablets, USP are indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

2. DOSAGE AND ADMINISTRATION

2.1. Adults

The usual initial antihypertensive oral dose of amlodipine besylate tablets is 5 mg once daily with a maximum dose of 10 mg once daily.

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

Adjust dosage 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.

The recommended dose for chronic stable or vasospastic angina is 5 to10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect . *[seeAdverse Reactions(6)]*

The recommended dose range for patients with coronary artery disease is 5 to10 mg once daily. In clinical studies, the majority of patients required 10 mg . *[seeClinical Studies(14.4)]*

2.2. Children

The effective antihypertensive oral dose in pediatric patients ages 6 to 17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients . *[seeClinical Pharmacology(12.4),Clinical Studies(14.1)]*

3. DOSAGE FORMS AND STRENGTHS

2.5 mg, 5 mg, and 10 mg Tablets

4. CONTRAINDICATIONS

Amlodipine besylate tablets are contraindicated in patients with known sensitivity to amlodipine.

5. WARNINGS AND PRECAUTIONS

5.1. Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.2. Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine besylate tablets, particularly in patients with severe obstructive coronary artery disease.

5.3. Beta-Blocker Withdrawal

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

5.4. Patients with Hepatic Failure

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine besylate to patients with severe hepatic impairment.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Amlodipine besylate tablets have been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine besylate tablets were well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine besylate tablets were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine besylate tablets (N= 1730) at doses up to

10 mg to placebo (N= 1250), discontinuation of amlodipine besylate tablets due to adverse reactions 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 edema. The incidence (%) of side effects that occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	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 that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

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

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	Amlodipine		Placebo	
Adverse Event	Male = % (N=1218)	Female = % (N=215)	Male = % (N=914)	Female = % (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitation	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <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:

arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Cardiovascular:**

hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Central and Peripheral Nervous System:**

anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **Gastrointestinal:**[1]

allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **General:**[1]

arthralgia, arthrosis, muscle cramps, myalgia. **Musculoskeletal System:**[1]

sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Psychiatric:**[1]

dyspnea, epistaxis. **Respiratory System:**[1]

angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular. **Skin and Appendages:**[11]

abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Special Senses:**

micturition frequency, micturition disorder, nocturia. **Urinary System:**

dry mouth, sweating increased. **Autonomic Nervous System:**

hyperglycemia, thirst. **Metabolic and Nutritional:**

leukopenia, purpura, thrombocytopenia. **Hemopoietic:**

These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies. [1]

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, 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, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

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.

In the CAMELOT and PREVENT studies , the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema. *[seeClinical Studies(14.4)]*

6.2. Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Amlodipine besylate tablets have been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

7. DRUG INTERACTIONS

7.1. In Vitro Data

data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin. *In vitro*

7.2. Cimetidine

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

7.3. 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.

7.4. Magnesium and Aluminum Hydroxide Antacid

Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of amlodipine

besylate tablets had no significant effect on the pharmacokinetics of amlodipine.

7.5. 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.

7.6. 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.

7.7. Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in 77 % increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patient on amlodipine to 20 mg daily

7.8. Digoxin

Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

7.9. Ethanol (Alcohol)

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

7.10. Warfarin

Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

7.11. CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

7.12. CYP3A4 Inducers

No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.

7.13. Drug/Laboratory Test Interactions

None known.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits

were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively, 8 times and 23 times the maximum recommended human dose of 10 mg on a mg/m basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. [222]

Based on patient weight of 50 kg. [2]

8.3. 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.

8.4. Pediatric Use

Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

8.5. Geriatric Use

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40 to 60%, and a lower initial dose may be required . *[seeDosage and Administration(2.1)]*

10. OVERDOSAGE

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

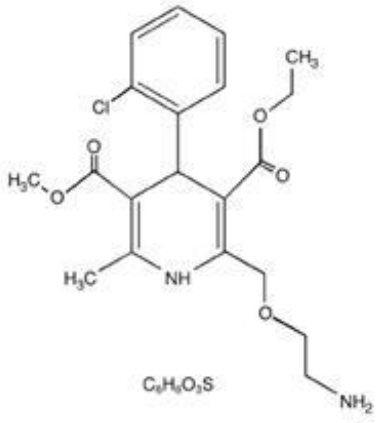
Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m basis) caused a marked peripheral vasodilation and hypotension. [2]

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

11. DESCRIPTION

Amlodipine besylate, USP is the besylate salt of amlodipine, a long-acting calcium channel blocker.

Amlodipine besylate, USP is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is C H CIN O • C H O S, and its structural formula is: 202525663



Amlodipine besylate, USP is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate tablets, USP are formulated as white tablets equivalent to 2.5 mg, 5 mg, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, USP each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine 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 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 ionized compound (pKa= 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. *in vitro*

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 mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, 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 A2 analog in experimental animal models and in human coronary vessels . This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal’s or variant) angina. *in vitro*

12.2. Pharmacodynamics

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, amlodipine besylate tablets 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 decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of 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 besylate tablets is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine besylate tablets 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.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine besylate tablets 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 hemodynamic studies, amlodipine besylate tablets have 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 normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine besylate tablets do not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg 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 besylate tablets and concomitant beta-blockers. In clinical studies in which amlodipine besylate tablets were administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters was observed. In clinical trials with angina patients alone, amlodipine besylate tablet therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

12.3. Pharmacokinetics and Metabolism

After oral administration of therapeutic doses of amlodipine besylate tablets, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine besylate tablets is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. 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 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. *Ex vivo*

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

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

12.4. Pediatric Patients

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine besylate tablets between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5 mg, 1.25 mg, or 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m basis, about twice the maximum recommended human dose. [2][3][2][3]

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose of 10 mg/day on a mg/m basis). [3][2]

Based on patient weight of 50 kg [3]

14. CLINICAL STUDIES

14.1. Effects in Hypertension

Adult Patients

The antihypertensive efficacy of amlodipine besylate tablets has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine besylate tablets and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours post dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. 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 were similar in black patients and in white patients.

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate tablets 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

14.2. Effects in Chronic Stable Angina

The effectiveness of 5 to 10 mg/day of amlodipine besylate tablets in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine besylate tablets, 354 placebo) with chronic stable angina. In 5 of the 8 studies,

significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine besylate tablets 10 mg, and averaged 7.9% (38 sec) for amlodipine besylate tablets 5 mg. amlodipine besylate tablets 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine besylate tablets 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).

14.3. Effects in Vasospastic Angina

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine besylate tablet therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 amlodipine besylate tablet and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

14.4. Effects in Documented Coronary Artery Disease

In PREVENT, 825 patients with angiographically documented coronary artery disease were randomized to amlodipine besylate tablets (5 to 10 mg once daily) or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine besylate tablets (5 to 10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the amlodipine besylate tablet and placebo groups, respectively, for a hazard ratio of 0.691 (95% CI: 0.540 to 0.884, $p = 0.003$). The primary endpoint is summarized in below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see). Effects in various subgroups are shown in . **Figure 1Table 1Figure 2**

In an angiographic substudy (n= 274) conducted within CAMELOT, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasound.

[IC] [/IC] **Figure 1 - Kaplan-Meier Analysis of Composite Clinical Outcomes for amlodipine versus Placebo**

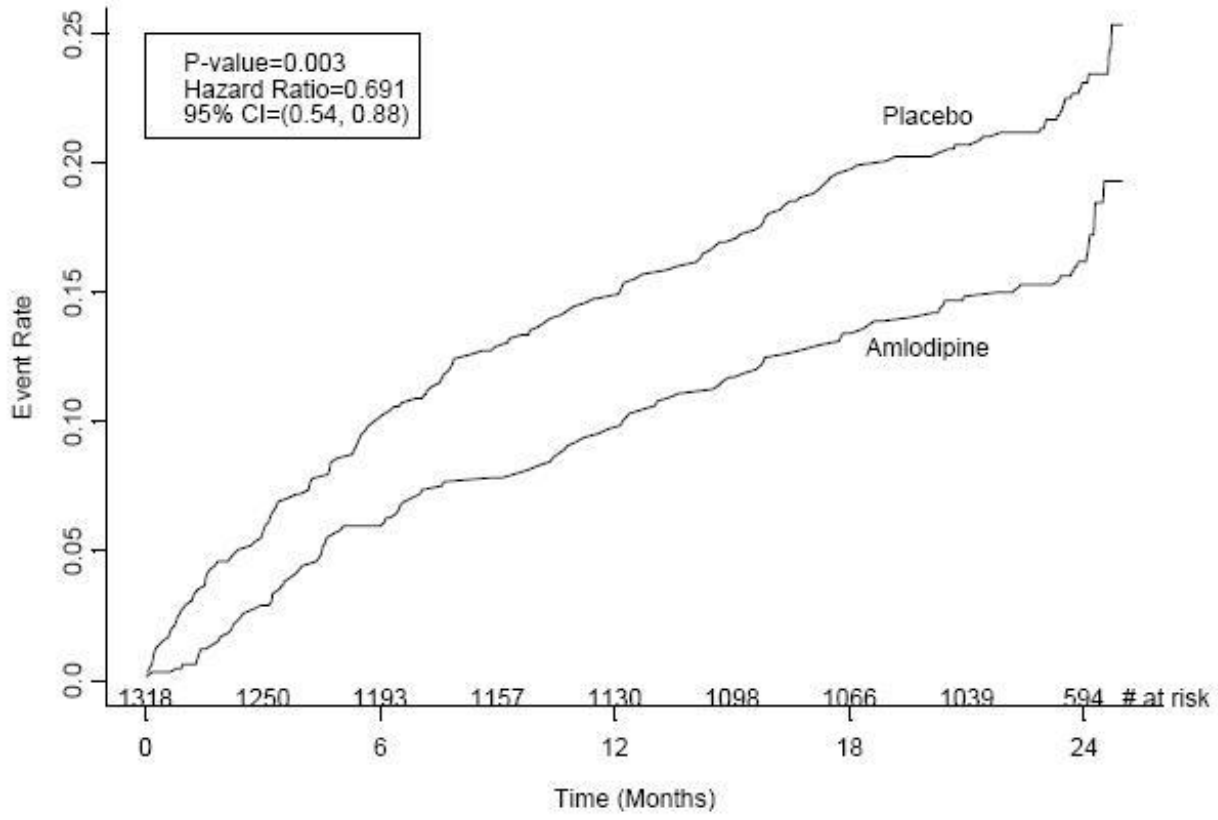


Figure 2 – Effects on Primary Endpoint of amlodipine versus Placebo across Sub-Groups

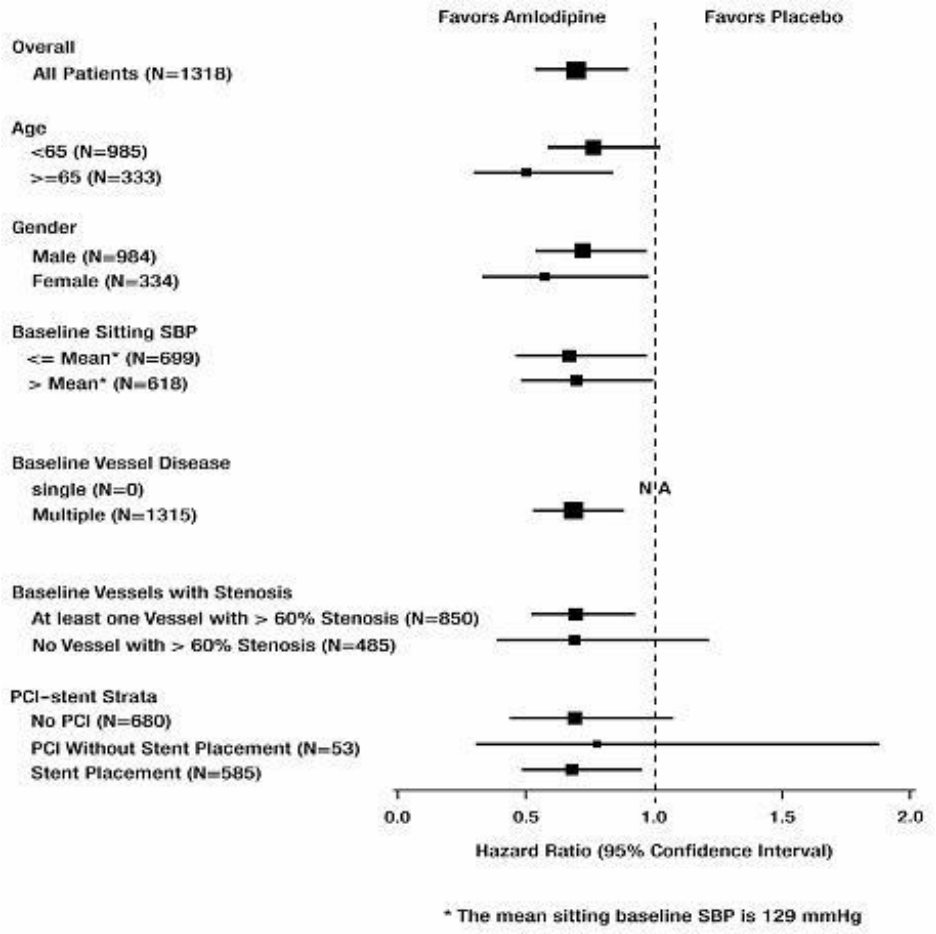


Table 1 below summarizes the significant composite endpoint and clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amlodipine and placebo.

Table 1.

Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	**NORVASC (N=663)**	**Placebo (N=655)**	**Risk Reduction (p-value)**
Composite CV Endpoint	**110 (16.6)**	**151 (23.1)**	**31% (0.003)**
Hospitalization for Angina *	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization *	78 (11.8)	103 (15.7)	27% (0.033)

Total patients with these events *

14.5. Studies in Patients with Heart Failure

Amlodipine besylate tablets have been compared to placebo in four 8 to 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 left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine besylate tablets 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 hospitalization 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 besylate tablets and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n= 827) or amlodipine besylate tablets (n= 827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine besylate tablets and placebo in the primary endpoint of all-cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine besylate tablets there were more reports of pulmonary edema.

AMLODIPINE BESYLATE TABLET

NDC: 50436-6624-1

AMLODIPINE BESYLATE

2.5 MG

30 TAB

WARNING:

KEEP OUT OF REACH OF CHILDREN

STORE AT 20-25°C (68-77°F)

CONTROLLED ROOM TEMPERATURE

MFG BY: CAMBER PHARM XXXXXXX

MFG NDC: 31722-0237-10

MFG LOT: XXXXXXX

LOT: XXXXXXX EXP: XXXXXXX

Pkg by: Unit Dose Services, LLC

Miami, FL 33179

NDC:50436-630 TAB
DRUG:AMLODIPINE BESYLATE 2.5 MG
LOT:XXXXXXX EXP:XXXXXXX

NDC:50436-630 TAB
DRUG:AMLODIPINE BESYLATE 2.5 MG
LOT:XXXXXXX EXP:XXXXXXX

NDC:50436-6624-1
DRUG:AMLODIPINE BESYLATE
LOT:XXXXXXX EXP:XXXXXXX

NDC:50436-630 TAB
DRUG:AMLODIPINE BESYLATE 2.5 MG
LOT:XXXXXXX EXP:XXXXXXX

AMLODIPINE BESYLATE

amlodipine besylate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:50436-6624(NDC:31722-237)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	2.5 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE	
ANHYDROUS DIBASIC CALCIUM PHOSPHATE	
SODIUM STARCH GLYCOLATE TYPE A POTATO	
MAGNESIUM STEARATE	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	237;IG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50436-6624-1	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077995	01/01/2011	

Labeler - Unit Dose Services (831995316)

Registrant - Unit Dose Services (831995316)

Establishment

Name	Address	ID/FEI	Business Operations
Unit Dose Services		831995316	REPACK(50436-6624)

Revised: 8/2012 Unit Dose Services