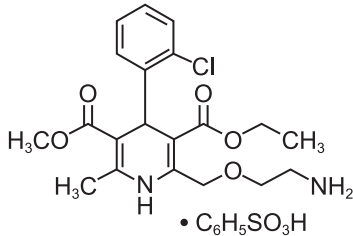


COMPOSITION

Each tablet contains: Amlodipine (as Besylate) BP/USP..... 5 & 10 mg, respectively.

DESCRIPTION

LEAF is the besylate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besylate 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 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 $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5O_3S$, and its structural formula is:



CLINICAL PHARMACOLOGY

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. 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. 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. 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 blocks constriction and restores blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in human coronary vessels. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

Pharmacodynamics:

Hemodynamics: 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. 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. In hypertensive patients with normal renal function, therapeutic doses of amlodipine results 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. Amlodipine is not associated with a negative inotropic effect when administered in the therapeutic dose range, even when co-administered with beta-blockers or agents possessing

significant negative inotropic effects in normal or well-compensated patients with heart failure.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction, even in patients receiving amlodipine and concomitant beta-blockers. Amlodipine has no adverse effects on electrocardiographic parameters when administered in combination with beta-blockers to patients with either hypertension or angina. With angina patients alone, amlodipine therapy does not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Pharmacokinetics:

Absorption: After oral administration of therapeutic doses of amlodipine, 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 is not altered by the presence of food.

Metabolism: 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. Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Elimination: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. 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 40–60%, and a lower initial dose may be required. A similar increase in AUC occurs in patients with moderate to severe heart failure.

INDICATIONS AND USAGE

Hypertension: Amlodipine (LEAF) is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). Amlodipine (LEAF) may be used alone or in combination with other antihypertensive agents.

Coronary Artery Disease (CAD):

Chronic Stable Angina: Amlodipine (LEAF) is indicated for the symptomatic treatment of chronic stable angina. Amlodipine (LEAF) may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina): Amlodipine (LEAF) is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine (LEAF) 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 (LEAF) is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

CONTRAINDICATIONS

Amlodipine (LEAF) is contraindicated in patients with known sensitivity to amlodipine.

ADVERSE REACTIONS

Most adverse reactions with amlodipine therapy are of mild or moderate severity. The most common side effects are edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence. The following events are rare to occur but are listed to alert the physician to a possible relationship:

System Organ Class**Adverse Drug Reactions**

General	Allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Cardiovascular	Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.
Central and Peripheral Nervous System	Hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
Gastrointestinal	Anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
Musculoskeletal System	Arthralgia, arthrosis, muscle cramps, myalgia.
Psychiatric	Sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System	Dyspnea, epistaxis.
Skin and Appendages	Angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.
Special Senses	Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System	Micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System	Dry mouth, increased sweating.
Metabolic and Nutritional	Hyperglycemia, thirst.
Hemopoietic	Leukopenia, purpura, thrombocytopenia.

Laboratory abnormalities:

Amlodipine therapy is not associated with clinically significant changes in routine laboratory tests.

DRUG INTERACTIONS**Impact of Other Drugs on Amlodipine:**

CYP3A Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers: No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Sildenafil: When amlodipine and sildenafil are used in combination, each agent independently exerts its own blood pressure lowering effect. Monitor for hypotension when sildenafil is co-administered with amlodipine.

Impact of Amlodipine on Other Drugs:

Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

USE IN SPECIFIC POPULATION

Pregnancy: There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation: No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production.

Pediatric Use: Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years. Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Geriatric Use: 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 40–60%, and a lower initial dose may be required.

WARNINGS AND PRECAUTIONS

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

Increased Angina or Myocardial Infarction: Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

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 (LEAF) to patients with severe hepatic impairment.

DOSAGE AND ADMINISTRATION

Adults: The usual initial antihypertensive oral dose of amlodipine (LEAF) is 5 mg once daily, and the maximum dose is 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency patients may be started on 2.5 mg once daily and this dose may be used when adding amlodipine (LEAF) to other antihypertensive therapy. Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary artery disease: The recommended dose range for patients with coronary artery disease is 5–10 mg once daily.

Children: The effective antihypertensive oral dose in pediatric patients (6–17 years) is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

OVERDOSAGE

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. If hypotension occurs, 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 with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15 - 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: LEAF Tablets 5 & 10 mg are available in packing containing 30 tablets, respectively.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔

15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

مشورہ ڈاکٹر کے نسخہ پر استعمال کریں۔

Complete Medical Information available only for doctors on request.



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