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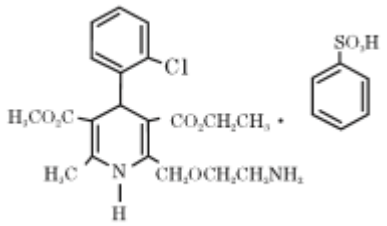
Package Insert of Amlodipine Besylate Tablets

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]
Generic Name: Amlodipine Besylate Tablets
Chinese Pinyin: Benhuangsuan Anlüdiping Pian

[Ingredients]
The active pharmaceutical ingredient (API) of this product is amlodipine besylate.
Chemical Name of the API: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate.
Structural Formula:



Molecular Formula: $C_{20}H_{25}N_2O_5Cl \cdot C_6H_6O_3S$
Molecular Weight: 567.1

[Properties]
This product is a white to off-white tablet.

[Indications]
1. Hypertension.
   This product is indicated for the treatment of hypertension, to lower blood pressure. It may be used alone or in combination with other antihypertensive agents.
2. Coronary Heart Disease（CAD）
   Chronic Stable Angina
   This product is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal agents.
   Vasospastic Angina （Prinzmetal's or Variant Angina）
   This product is indicated for the treatment of confirmed or suspected vasospastic angina. IT may be used alone or in combination with other antianginal agents.

[Strength]
5 mg (amlodipine free base）

[Dosage and Administration]
Adults: The usual initial antihypertensive oral dose of this product is 5 mg once daily, and the maximum dose is 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 this product 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.

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

In combination with other antihypertensive agents and/or anti-anginal drugs, amlodipine is safe to use in combination with thiazide diuretics, ACEI, β-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

[Adverse Reactions]

Foreign clinical trials displayed that amlodipine besylate has been evaluated for safety in more than 11,000 patients. In general, treatment with this product was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy were of mild or moderate severity. The most commonly reported side effects more frequent than placebo are reflected in the table below. The incidence (%) of side effects that occurred in a dose related manner are as follows:

	Amlodipine			**Placebo**
	2.5 mg	**5 mg**	**10 mg**	**2.5 mg**
	N=275	**N=296**	**N=268**	**N=275**
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 reactions that were not clearly dose related but were reported with an incidence greater than 1% in placebo-controlled clinical trials include the following:

	Amlodipine (%)	**Placebo (%)**
	(N=1730)	**(N=1250)**
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**	
	Male=%	**Female=%**	**Male=%**	**Female=%**

	(N=1218)	(N=512)	(N=914)	(N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	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:

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.

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

Musculoskeletal System: arthralgia, arthrosis, muscle cramps**, myalgia.

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

Respiratory System: dyspnea**, epistaxis.

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

**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.

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

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred < 0.1%: heart failure, arrhythmia, premature, skin discoloration, urticaria, dry skin, alopecia, dermatitis, muscle weakness, twitching, ataxia, too strong muscle tension , migraine, cool skin, apathy, irritability, forgetfulness, gastritis, appetite increases, liquid stools, cough, coryza, dysuria, urinary, olfactory dysfunction, dysgeusia, abnormal vision, dry eye.

Other adverse reactions are difficult to distinguish with the use of the function or accompanying diseases, such as myocardial infarction or 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 [see Clinical Studies], the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema. 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 has 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.

[Contraindications]
This product is contraindicated in patients who are allergic to dihydropyridines or any ingredients in this product.

[Precautions]

1. **Warning:** extremely few patients, particularly those who were complicated by severe obstructive coronary artery diseases, experienced an increase in the frequency/duration and/or severity of angina, or experienced acute myocardial infarction when beginning calcium antagonist treatment or after dose increment. The mechanism for this has not yet been clearly determined.
2. This product produces a vasodilatory effect gradually. There were rare reports of acute hypotension following administration of this product. In patients with severe aortic stenosis, attention should be given to the combination of this product with other peripheral vasodilators.
3. **Use in patients with heart failure:** vigilance is called for when using calcium antagonists in patients with congestive heart failure. Although noticeable difference were not found in the incidence of heart failure worsening between this product and the placebo in a long-term, placebo-controlled clinical study (PHASE-2) among patients with non-ischemic heart failure (NYHA grade III-IV), there were an increased number of reports of pulmonary edema related to amlodipine.
4. **Use in patients with hepatic impairment:** like all other calcium antagonists the half-life of this product will be prolonged in patients with hepatic impairment. The recommended dose of this product in this kind of patients has not been determined. Therefore, vigilance is called for when using this product in such patients.
5. **Use in patients with renal failure:** the plasma concentration of amlodipine is not related to the degree of renal impairment and therefore, the usual dose can be used. This product cannot be removed from the body through dialysis.
6. **Withdrawal of β-receptor blockers:** amlodipine is not a β-receptor blocker and therefore does not provide protection against the risk associated with sudden withdrawal of β-receptor blockers. Any β-receptor blocker should be withdrawn gradually.

[Use in Pregnant and Nursing Mothers]

There are no adequate and well-controlled studies in pregnant women. According to the results of animal experimentation, this product can be used by pregnant women only when it is highly necessary. 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 this product is administered.

[Pediatric Use]

The recommended dosage of this product for children patients with hypertension aged between 6 and 17 is 2.5 - 5 mg, q.d. No studies of this product given at a dose over 5 mg daily have been conducted in children patients. Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

[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 40–60%, and a lower initial dose may be required *[see Dosage and Administration]*.

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

Impact of other drugs on amlodipine :
Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

Impact of amlodipine on other drugs :
Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Clinical studies have confirmed that this product is safe when it co-administered with thiazide diuretics, β-adrenergic receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroid anti-inflammatory drugs (NSAIDs), antibiotics and oral anti –diabetic drugs.

The interaction with laboratory examination: it is not clear.

[Over-Dosage]

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 mgamlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

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. Reports of deliberate excessive over-dosage showed that one patient ingested 250 mg of amlodipine was asymptomatic and not hospitalized for treatment. Another patient (ingested 120 mg) was hospitalized for gastric lavage, and the patient's blood pressure maintained a normal level. A third patient (ingested 105 mg) was hospitalized and found to have a complication hypotension of 90/50 mm Hg, which returned to normal after plasma volume expansion. There are records on a case of accidental over-dosage in which a 19-month old baby body was accidently administered 30 mg of amlodipine (approximately equal to 2 mg/kg of body weight). During the period of emergency treatment, the vital signs of the baby were stable, without hypotension, but his heart rate reached 180 bpm. Ipecac was administered 3.5 hours later, and there was no record of sequelae in subsequent observations throughout the night.

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 this product is highly protein bound, hemodialysis is not likely to be of benefit.

[Parmacology and Txicology]

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. 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 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 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 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 in vitro. 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. 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 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).

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.

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

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 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 effects 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.

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, 1.25, and 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/m2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about twice the maximum recommended human dose.

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 dose3 of 10 mg/day on a mg/m2 basis).

[Pharmacokinetics]
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.

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. Ex vivo 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 30–50 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 was observed in patients with moderate to severe heart failure.

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 7 tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 7 tablets/plate, two plates/carton
Aluminum-plastic blister packaging, 7 tablets/plate, three plates/carton
Aluminum-plastic blister packaging, 7 tablets/plate, four plates/carton
Aluminum-plastic blister packaging, 10tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 10tablets/plate, two plates/carton

[Shelf-Life]
36 months

[Executive Standard]
Chinese Pharmacopoeia 2015 Edition Second Part

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Guo Yao Zhun Zi H20093746

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