

# LEVAMLODIPINE- levamlodipine tablet

## Xspire Pharma, LLC

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVAMLODIPINE TABLETS safely and effectively. See full prescribing information for LEVAMLODIPINE TABLETS.

### LEVAMLODIPINE TABLETS, for oral use.

#### Initial U.S. Approval: 2019

#### INDICATIONS AND USAGE

LEVAMLODIPINE TABLETS is calcium channel blocker and may be used alone or in combination with other antihypertensive agents 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. (1)

#### DOSAGE AND ADMINISTRATION

- Adult recommended starting dose: 2.5 mg orally once daily with maximum dose 5 mg once daily. ( 2.1)
  - Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 1.25 mg once daily. ( 2.1)
- Pediatric starting dose: 1.25 mg to 2.5 mg once daily. ( 2.2)

**Important Limitation:** Doses in excess of 2.5 mg daily have not been studied in pediatric patients. ( 2.2)

#### DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg (functionally scored), and 5 mg, 2.5 mg tablets can be split for 1.25 mg dose. ( 3)

#### CONTRAINDICATIONS

- Known sensitivity to amlodipine. ( 4)

#### WARNINGS AND PRECAUTIONS

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely. ( 5.1)
- 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. ( 5.2)
- Titrate slowly in patients with severe hepatic impairment. ( 5.3)

#### ADVERSE REACTIONS

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

**To report SUSPECTED ADVERSE REACTIONS, call Xspire Pharma LLC at 1-888-252-3901 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### DRUG INTERACTIONS

- Do not exceed doses greater than 20 mg daily of simvastatin. ( 7.2)

#### USE IN SPECIFIC POPULATIONS

- 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. ( 8.5)

See 17 for FDA-approved patient labeling.

Revised: 11/2021

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## **FULL PRESCRIBING INFORMATION**

### **1. INDICATIONS AND USAGE**

#### **1.1 Hypertension**

LEVAMLODIPINE TABLETS is indicated for the treatment of hypertension in adults and pediatric patients 6 years and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including levamlodipine.

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).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Levamlodipine may be used alone or in combination with other antihypertensive agents.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Adults**

The usual initial antihypertensive oral dose of levamlodipine is 2.5 mg once daily, and the maximum dose is 5 mg once daily.

Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 1.25 mg once daily and this dose may be used when adding levamlodipine 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.

## **2.2 Children**

The effective antihypertensive oral dose in pediatric patients ages 6–17 years is 1.25 mg to 2.5 mg once daily. Doses in excess of 2.5 mg daily have not been studied in pediatric patients [see *Clinical Pharmacology (12.4)*, *Clinical Studies (14.1)*].

## **3 DOSAGE FORMS AND STRENGTHS**

Tablet, 2.5 mg is white to off-white, capsule shaped, flat-faced tablet with functional score on each side, engraved with "OE" on one side and "B47" on the other side.

Tablet of 2.5 mg can be split for 1.25 mg dose for medical conditions that need 1.25 mg dose.

Tablet, 5 mg is white to off-white, soap shaped, flat-faced tablet, engraved with "OE" on one side and "B48" on the other side.

## **4 CONTRAINDICATIONS**

Levamlodipine is 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, particularly in patients with severe obstructive coronary artery disease.

### **5.3 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 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 has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine besylate was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with

amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine besylate (N = 1730) at doses up to 10 mg to placebo (N = 1250), discontinuation of amlodipine besylate because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). 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:

	<b>Amlodipine</b>			<b>Placebo</b>
	<b>2.5mg N=275</b>	<b>5mg N=296</b>	<b>10mg N=268</b>	<b>N=520</b>
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 1.0% in placebo-controlled clinical trials include the following:

	<b>Amlodipine (%) (N=1730)</b>	<b>Placebo (%) (N=1250)</b>
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:

	<b>Amlodipine (%)</b>		<b>Placebo (%)</b>	
	<b>Male = % (N=1218)</b>	<b>Female = % (N=512)</b>	<b>Male = % (N=914)</b>	<b>Female = % (N=336)</b>
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, <sup>1</sup> back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

**Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, <sup>1</sup> myalgia.

**Psychiatric:** sexual dysfunction (male <sup>1</sup> and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

**Respiratory System:** dyspnea, <sup>1</sup> epistaxis.

**Skin and Appendages:** angioedema, erythema multiforme, pruritus, <sup>1</sup> rash, <sup>1</sup> 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, sweating increased.

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

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

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 of amlodipine in coronary artery disease, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

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<sup>1</sup> 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.

## 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.

Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and 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.

## 7 DRUG INTERACTIONS

### 7.1 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 [see *Clinical Pharmacology (12.3)*]

#### ***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***

Monitor for hypotension when sildenafil is co-administered with amlodipine [see *Clinical Pharmacology (12.2)*].

### 7.2 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 [see *Clinical Pharmacology (12.3)*].

#### ***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 [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The limited available data based on post-marketing reports with amlodipine use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy [see *Clinical Considerations*]. In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine during organogenesis at doses approximately 10 and 20-times the maximum recommended human dose (MRHD), respectively. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of

labor in rats at this dose [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

### Clinical Considerations

#### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

### Data

#### *Animal Data*

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

## **8.2 Lactation**

### Risk Summary

Limited available data from a published clinical lactation study reports that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. 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.

## **8.4 Pediatric Use**

Levamlodipine (1.25 to 2.5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years [see *Clinical Studies (14.1)*]. Effect of levamlodipine 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 40–60%, and a lower initial dose may be required [see *Dosage 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.

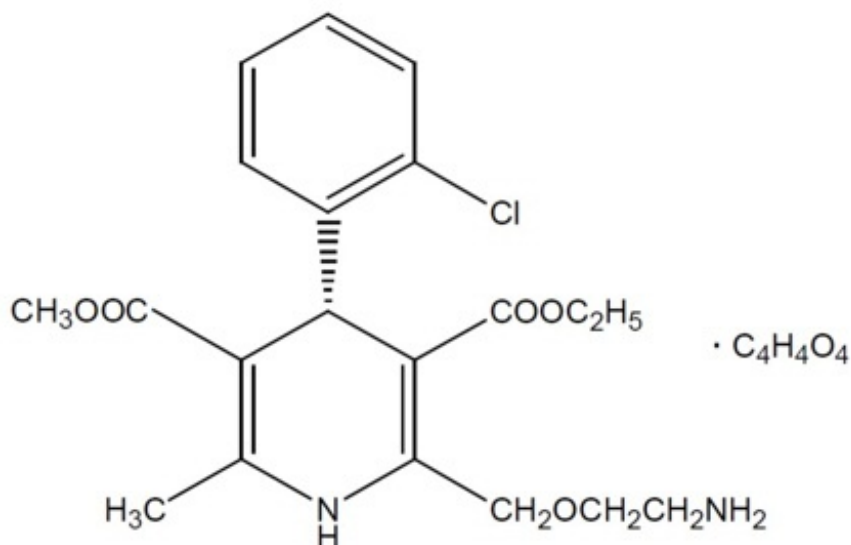
Single oral doses of amlodipine equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a  $\text{mg}/\text{m}^2$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

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

The active ingredient levamlodipine maleate is the maleate salt of levamlodipine, the pharmacologically active isomer of amlodipine, a long-acting calcium channel blocker.

Levamlodipine maleate is chemically described as (S)-3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate maleate, and its structural formula is:



Levamlodipine maleate is an off-white to light yellow crystalline powder with a molecular weight of 524.95. It is slightly soluble in water and sparingly soluble in ethanol. LEVAMLODIPINE TABLETS are formulated as white to off-white tablets containing 2.5, and 5 mg of levamlodipine (equivalent to 3.2, and 6.4 mg of levamlodipine maleate respectively), for oral administration. In addition to the active ingredient, levamlodipine maleate, each tablet contains the following inactive ingredients: betadex, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and pregelatinized starch .

## **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 *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 ( $pK_a=8.6$ ), 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.

Amlodipine is a 1:1 racemic mixture of levamlodipine and dextro amlodipine, it has been demonstrated that levamlodipine is the pharmacologically active, anti-hypertensive isomer.

### **12.2 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.

### Drug Interactions

*Sildenafil:* When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect [see *Drug Interactions (7.1)*].

## **12.3 Pharmacokinetics**

The exposure ( $C_{max}$  and AUC) of levamlodipine is similar between LEVAMLODIPINE TABLETS 5 mg and Norvasc<sup>®</sup> (amlodipine besylate) 10 mg under fasting condition.

### Absorption

After oral administration of LEVAMLODIPINE 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 LEVAMLODIPINE TABLETS is not altered by the presence of food.

### Distribution

*Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

### 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.

## Excretion

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.

## Specific Populations

### *Renal Impairment*

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

### *Hepatic Impairment*

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.

## **12.4 Pediatric Patients**

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

## 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.

*CYP3A 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 CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent [see *Drug Interactions (7.1)*].

### *Impact of amlodipine on other drugs*

Amlodipine is a weak inhibitor of CYP3A and may increase exposure to CYP3A substrates.

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

*Simvastatin:* Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone [see *Drug Interactions (7.2)*].

*Cyclosporine:* A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine [see *Drug Interactions (7.2)*].

*Tacrolimus*: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs [see *Drug Interactions (7.2)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Rats and mice treated with amlodipine 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/m<sup>2</sup> basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.<sup>2</sup> For the rat, the highest dose was, on a mg/m<sup>2</sup> basis, about twice the maximum recommended human dose.<sup>2</sup>

Mutagenicity studies conducted with amlodipine 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 (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<sup>2</sup> of 10 mg/day on a mg/m<sup>2</sup> basis).

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<sup>2</sup> Based on patient weight of 50 kg

## **14 CLINICAL STUDIES**

### **14.1 Effects in Hypertension**

#### Adult Patients

The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, 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 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.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### *2.5 mg Tablets*

Levamlodipine – 2.5 mg tablets are supplied as white to off-white, capsule shaped, flat-faced tablet with functional score on each side, engraved with "OE" on one side and "B47" on the other side and supplied as follows:

NDC 42195-425-30-30 Bottle of 30 tablets with child-resistant closure

### *5 mg Tablets*

Levamlodipine – 5 mg tablets are supplied as white to off-white, soap shaped, flat-faced tablet, engraved with "OE" on one side and "B48" on the other side and supplied as follows:

NDC 42195-450-30 Bottle of 30 tablets with child-resistant closure

### Storage

Store bottles at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in tight, light-resistant containers (USP).

Manufactured by:

**CSPC Ouyi Pharmaceutical Co., Ltd.**  
**Shijiazhuang, Hebei, China, 052160**

Distributed by:

**Xspire Pharma LLC**  
**Ridgeland, MS 39157**

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### **PATIENT INFORMATION LEVAMLODIPINE TABLETS**

#### **What is LEVAMLODIPINE TABLETS?**

LEVAMLODIPINE TABLETS is a prescription medicine used to treat high blood pressure (hypertension) in adults and pediatric patients 6 years and older. LEVAMLODIPINE TABLETS can be used by itself or with other high blood pressure medicines. It is not known if LEVAMLODIPINE TABLETS is safe and effective in children less than 6 years of age.

**Do not take LEVAMLODIPINE TABLETS** if you are allergic to amlodipine or to any of the ingredients in LEVAMLODIPINE TABLETS. See the end of this Patient Information for a complete list of ingredients in LEVAMLODIPINE TABLETS.

**Before taking LEVAMLODIPINE TABLETS, tell your healthcare provider about all of your medical conditions, including if you:**

- have heart problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if LEVAMLODIPINE TABLETS can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with LEVAMLODIPINE TABLETS.
- are breastfeeding or plan to breastfeed. LEVAMLODIPINE TABLETS can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LEVAMLODIPINE TABLETS.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**How should I take LEVAMLODIPINE TABLETS?**

- Take LEVAMLODIPINE TABLETS exactly as your healthcare provider tell you to.
- Take LEVAMLODIPINE TABLETS 1 time a day.
- If you take too much LEVAMLODIPINE TABLETS, contact your local poison control center or go to the nearest hospital emergency room right away.

**What are the possible side effects of LEVAMLODIPINE TABLETS?**

**LEVAMLODIPINE TABLETS may cause serious side effects, including :**

- **Low blood pressure (hypotension).** LEVAMLODIPINE TABLETS may cause low blood pressure, especially in people that have a condition called severe aortic stenosis. Tell your healthcare provider if you feel faint or lightheaded.
- **Worsening chest pain (angina) or heart attack.** LEVAMLODIPINE TABLETS may cause worsening chest pain or heart attack after starting or increasing your dose, especially in people with a condition called severe obstructive coronary artery disease. If that happens, call your healthcare provider right away or go directly to a hospital emergency room.

**The most common side effects of LEVAMLODIPINE TABLETS include:**

- swelling of your legs or ankles
- tiredness
- nausea
- stomach pain
- sleepiness
- dizziness
- flushing (hot or warm feeling in your face)
- heart palpitations (very fast heartbeat)

These are not all of the possible side effects of LEVAMLODIPINE TABLETS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store LEVAMLODIPINE TABLETS?**

- Store LEVAMLODIPINE TABLETS at 68°F to 77°F (20°C to 25°C).
- Keep LEVAMLODIPINE TABLETS out of the light.

**Keep LEVAMLODIPINE TABLETS and all medicines out of the reach of children.**

## General information about the safe and effective use of LEVAMLODIPINE TABLETS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LEVAMLODIPINE TABLETS for a condition for which it was not prescribed. Do not give LEVAMLODIPINE TABLETS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LEVAMLODIPINE TABLETS that is written for health professionals.

### What are the ingredients in LEVAMLODIPINE TABLETS?

**Active ingredient:** levamlodipine maleate

**Inactive ingredients:** betadex, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and pregelatinized starch

Manufactured by:  
CSPC Ouyi Pharmaceutical Co., Ltd.

Distributed by:  
Xspire Pharma LLC  
Ridgeland, MS 39157  
For more information, call Toll Free number 1-888-252-3901

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued:  
08/2021

## PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Label

NDC 42195-425-30

Levamlodipine Tablets

2.5 mg\*

30 Tablets

Rx only

CSPC

Xspire Pharma LLC

<p>*Each tablet contains 2.5 mg of levamlodipine (equivalent to 3.2 mg of levamlodipine maleate). Recommended dosage: See prescribing information. Dispense in tight, light-resistant containers (USP). Manufactured by: CSPC Ouyi Pharmaceutical Co., Ltd. Shijiazhuang, Hebei, China, 052160</p>	<p>This package is child-resistant. Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT. Distributed by: Xspire Pharma LLC Ridgeland, MS 39157</p>	<p>NDC 42195-425-30 Levamlodipine Tablets <b>2.5 mg*</b> 30 Tablets Rx only CSPC Xspire Pharma</p>	<p>6 4219542530 3</p>
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# PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

NDC 42195-450-30

Levamlodipine Tablets

5 mg\*

30 Tablets

Rx only

CSPC

Xspire Pharma LLC

<p>*Each tablet contains 5 mg of levamlodipine (equivalent to 6.4 mg of levamlodipine maleate). Recommended dosage: See prescribing information. Dispense in tight, light-resistant containers (USP). Manufactured by: CSPC Ouyi Pharmaceutical Co., Ltd. Shijiazhuang, Hebei, China, 052160</p>	<p>This package is child-resistant. Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT.</p>	<p>NDC 42195-450-30</p>	
<p>Distributed by: Xspire Pharma LLC Ridgeland, MS 39157</p>	<p>Rev. 08/2021</p>	<p>Levamlodipine Tablets</p>	
	<p>GTIN SN EXP LOT</p>	<p>5 mg*</p>	
		<p>30 Tablets</p>	<p>Rx only</p>
			

## LEVAMLODIPINE

levamlodipine tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42195-425
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LEVAMLODIPINE MALEATE</b> (UNII: 12VW9T2ITA) (LEVAMLODIPINE - UNII:0P6NLP6806)	LEVAMLODIPINE MALEATE	2.5 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>BETADEX</b> (UNII: JV039JZZ3A)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	

### Product Characteristics

<b>Color</b>	white (white to off-white)	<b>Score</b>	2 pieces
<b>Shape</b>	OVAL	<b>Size</b>	12mm
<b>Flavor</b>		<b>Imprint Code</b>	OE;B47
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42195-425-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/15/2021	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA212895	08/15/2021	

## LEVAMLODIPINE

levamlodipine tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42195-450
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LEVAMLODIPINE MALEATE</b> (UNII: 12VW9T2ITA) (LEVAMLODIPINE - UNII:0P6NLP6806)	LEVAMLODIPINE MALEATE	5 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>BETADEX</b> (UNII: JV039JZZ3A)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	

### Product Characteristics

<b>Color</b>	white (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	OVAL	<b>Size</b>	12mm
<b>Flavor</b>		<b>Imprint Code</b>	OE;B48
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42195-450-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/15/2021	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA212895	08/15/2021	

**Labeler** - Xspire Pharma, LLC (078312042)

## Establishment

Name	Address	ID/FEI	Business Operations
CSPC OUYI PHARMACEUTICAL CO., LTD		421303775	manufacture(42195-425, 42195-450)

Revised: 11/2021

Xspire Pharma, LLC