RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	Conjupri™
Generic Name	levamlodipine
Drug Manufacturer	CSPC Ouyi Pharmaceutical Co. Ltd.

New Drug Approval

FDA Approval Date: December 19, 2019
Review Designation: Standard
Type of Review: Type 2 - New Active Ingredient and Type 3 - New Dosage Form
Dispensing Restrictions: Open Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

High blood pressure is a common condition in which the long-term force of the blood against your artery walls is high enough that it may eventually cause health problems, such as heart disease.

Blood pressure is determined both by the amount of blood your heart pumps and the amount of resistance to blood flow in your arteries. The more blood your heart pumps and the narrower your arteries, the higher your blood pressure.

In the United States, about 77.9 million (1 out of every 3) adults have high blood pressure.
Data from NHANES 2007–10 showed that of those with high blood pressure:

- 81.5 percent are aware they have it.
- 74.9 percent are under current treatment.
- 52.5 percent have it controlled.
- 47.5 percent do not have it controlled.
- Among adults age 20 and older in the United States, the following have high blood pressure:
    - For non-Hispanic whites, 33.4 percent of men and 30.7 percent of women.
    - For non-Hispanic blacks, 42.6 percent of men and 47.0 percent of women.
    - For Mexican Americans, 30.1 percent of men and 28.8 percent of women.

Efficacy

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 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 2.5 mg 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.

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

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

CONTRAINDICATIONS

Levamlodipine is contraindicated in patients with known sensitivity to amlodipine.

Clinical Pharmacology

MECHANISMS 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.

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.

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Dose & Administration

ADULTS

2.5 mg orally once daily with maximum dose 5 mg once daily.

Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 1.25 mg once daily.

PEDIATRICS

Age ≥ 6 years: 1.25 mg to 2.5 mg once daily

Important Limitation: Doses > 2.5 mg daily have not been studied in pediatric patients.

GERIATRICS

Refer to adult dosing.

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.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 1.25 mg, 2.5 mg, 5 mg