

Chiral Antihypertensive Agent LODIEN® Tab. 2.5mg (S-Amlodipine Nicotinate). **COMPOSITION.** Each tablet contains Active: S-Amlodipine Nicotinate 3.253mg (as S-Amlodipine: 2.5mg) [APPEARANCE]. White pentagonal tablet

INDICATIONS AND USAGE

1. Hypertension. LODIEN is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
2. Chronic Stable Angina. LODIEN is indicated for the treatment of chronic stable angina. LODIEN may be used alone or in combination with other antianginal agents.
3. Vasospastic Angina (Prinzmetal's or Variant Angina). LODIEN is indicated for the treatment of confirmed or suspected vasospastic angina. LODIEN may be used as monotherapy or in combination with other antianginal drugs.

DOSAGE AND ADMINISTRATION. Adults: The usual initial antihypertensive oral dose of LODIEN is 2.5 mg once daily with a maximum dose of 5 mg once daily. Dosage should be adjusted according to each patient's need.

CONTRAINDICATION. LODIEN is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS. Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS. General: Since the vasodilation induced by LODIEN is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering LODIEN, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. LODIEN (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). LODIEN has been compared to placebo in four 8-12 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 LVEF.

Beta-Blocker Withdrawal: LODIEN 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. Patients with Hepatic Failure: Since LODIEN is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering LODIEN to patients with severe hepatic impairment. Drug Interactions: In vitro data indicate that LODIEN has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin. Effect of other agents on LODIEN CIMETIDINE: Co-administration of LODIEN with cimetidine did not alter the pharmacokinetics of LODIEN. 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. MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of LODIEN had no significant effect on the pharmacokinetics of LODIEN. SILDENAFIL: A single 100 mg dose of sildenafil (Viagra[®]) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of LODIEN. When LODIEN and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect. Effect of LODIEN on other agents ATORVASTATIN: Co-administration of multiple 10 mg doses of LODIEN with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. DIGOXIN: Co-administration of LODIEN with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. ETHANOL (alcohol): Single and multiple 10 mg doses of LODIEN had no significant effect on the pharmacokinetics of ethanol. WARFARIN: Co-administration of LODIEN with warfarin did not change the warfarin prothrombin response time. In clinical trials, LODIEN has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. Drug/Laboratory Test Interactions: None known. _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 levels. 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 of 10 mg/day on a mg/m² basis). Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate as 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/m² 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. 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. *Based on patient weight of 50 kg. _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 LODIEN is administered. Pediatric Use: The effect of LODIEN on blood pressure in patients less than 6 years of age is not known. Geriatric Use: Clinical studies of LODIEN 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. **ADVERSE REACTIONS** Treatment with LODIEN was well-tolerated. In controlled clinical trials directly comparing amlodipine and placebo, the most common side effects are as follows: Autonomic Nervous System: flushing. General: fatigue. Cardiovascular: edema Central and Peripheral Nervous System: dizziness, headache Gastrointestinal: abdominal pain, nausea. Heart beat rate: palpitations. Psychiatric: somnolence. 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, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. Gastrointestinal: anorexia, constipation, dyspepsia,** 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 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. LODIEN 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. 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. LODIEN

has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **OVERDOSAGE.** 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 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/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 LODIEN is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. _If massive overdose should occur; active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As LODIEN is highly protein bound, hemodialysis is not likely to be of benefit. **HOW SUPPLIED.** LODIEN[®] Tab. 2.5mg (S-amlodipine nicotinate equivalent to 2.5 mg of S-amlodipine per tablet) is white pentagonal tablet engraved with "HL" on one side and "S" on the other side. Store boxes at room temperature (1~30?) in tightly sealed containers.