AMLONEXT™

(USP Specification)

Amlodipine

(BP Specification)

5mg Tablets

COMPOSITION

AMLONEXT 5mg Tablets : Each tablet contains:
Amlodipine (as besylate) 5mg
(USP Specification)

DESCRIPTION

AMLONEXT is the besylate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2 aminoethoxy) methyl] 4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarbo-xylate, monobenzene
Sulphonate.

INDICATIONS

Coronary Artery Disease, Chronic Stable Angina, Vasospastic Angina (Prinzmetal's or Variant Angina), Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%.

DOSAGE AND ADMINISTRATION

Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily.
Pediatric starting dose: (age 6-17) 2.5 mg to 5 mg once daily. Important Limitation: Doses in excess of 5 mg daily have not been studied in pediatric patients.

CLINICAL PARTICULARS

Pharmacodynamics:

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but Amlodipine reduces total ischemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (prinzmetals or variant angina).

Pharmacokinetics:

Absorption:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absorption of amlodipine is not influenced by concomitant food intake. Absolute bioavailability of the unchanged active substance is estimated to be 64 80%.Peak plasma levels are reached 6-12 hours after administration.

Distribution:

The volume of distribution is approximately 21 l/kg. The pKa of amlodipine is 8.6. In vitro studies have shown that amlodipine is bound to plasmatic proteins up to 97.5%.

Biotransformation:

Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound.

Elimination:

The plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. 60% of metabolites are excreted in the urine.

Hepatic impairment:

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly:

The time to reach peak plasma concentrations is similar in elderly and younger patients. The clearance tends to be decreased with resulting increases in (AUC) and terminal elimination half-life in elderly patients. Increase in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

ADVERSE REACTIONS

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, 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, sweating increased.
Metabolic and Nutritional: hyperglycemia, thirst.

CONTRAINDICATIONS

AMLONEXT is contraindicated in patients with known sensitivity to amlodipine.

PRECAUTIONS AND WARNINGS

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 **AMLONEXT**, particularly in patients with severe obstructive coronary artery disease.

Beta-Blocker Withdrawal:

AMLONEXT 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 Because **AMLONEXT** 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 **AMLONEXT** to patients with severe hepatic impairment.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Pregnancy Category C, 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.

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 **AMLONEXT** is administered.

Pediatric Use:
Effect of **AMLONEXT** on blood pressure in patients less than 6 years of age is not known.

Geriatric Use:
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.

DRUG INTERACTIONS

In Vitro Data:
In vitro data indicate that **AMLONEXT** has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Cimetidine:
Co-administration of **AMLONEXT** with cimetidine did not alter the pharmacokinetics of **AMLONEXT**.

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.

Magnesium and Aluminum Hydroxide Antacid:
Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of **AMLONEXT** had no significant effect on the pharmacokinetics of **AMLONEXT**.

Sildenafil:
A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of **AMLONEXT**. When **AMLONEXT** and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin:
Co-administration of multiple 10 mg doses of **AMLONEXT** with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin:
Co-administration of **AMLONEXT** with digoxin did not change serum digoxin levels or digoxin renal clearance in normal
Volunteers.

Ethanol (Alcohol):
Single and multiple 10 mg doses of **AMLONEXT** had no significant effect on the pharmacokinetics of ethanol.

Warfarin:
Co-administration of **AMLONEXT** with warfarin did not change the warfarin prothrombin response time.

CYP3A4 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 CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers:
No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when Amlodipine is co-administered with CYP3A4 inducers.

Drug/Laboratory Test Interactions:
None known.

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 **AMLONEXT** is limited. 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 **AMLONEXT** is highly protein bound, hemodialysis is not likely to be of benefit.

STORAGE
Store at 20°C - 25°C. Protect from light and moisture.
(Excursions permitted to 15°C - 30°C)

HOW SUPPLIED
AMLONEXT 5 mg Tablets: Pack of 20 tablets.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

PLEASE READ THE CONTENTS CAREFULLY BEFORE USE. THIS PACKAGE INSERT IS CONTINUALLY UPDATED FROM TIME TO TIME.

Lactose & Gluten Free

NEXT PHARMACEUTICAL
Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
Plot no. 44-A&B, Sunder Industrial Estate Lahore-Pakistan