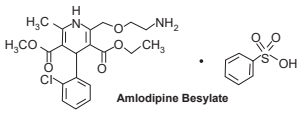
M-LOW™ PLUS

[Amlodipine + Hydrochlorothiazide]

ایم۔ لو پلس

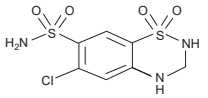
Tablets 5mg+12.5mg & 10mg+12.5mg

DESCRIPTION
M-Low Plus (Amlodipine + Hydrochlorothiazide) is a combination of Amlodipine, a long acting calcium channel blocker and Hydrochlorothiazide, a diuretic. Chemically Amlodipine Besylate is 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4 dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ and the structural formula is:



Amlodipine Besylate

Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and the structural formula is:



Hydrochlorothiazide

QUALITATIVE & QUANTITATIVE COMPOSITION
M-Low Plus (Amlodipine + Hydrochlorothiazide) is available for oral administration as:

M-Low Plus Tablets 5mg+12.5mg
Each tablet contains:
Amlodipine... 5mg
(as Amlodipine Besylate USP)
Hydrochlorothiazide USP... 12.5mg

M-Low Plus Tablets 10mg+12.5mg
Each tablet contains:
Amlodipine... 10mg
(as Amlodipine Besylate USP)
Hydrochlorothiazide USP... 12.5mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Amlodipine
The mechanism of the antihypertensive action of amlodipine 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:

1. 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.
2. 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 dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium.

Pharmacokinetics
Absorption
Amlodipine
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64% and 80%. The bioavailability of amlodipine is not affected by food intake.

Hydrochlorothiazide
Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65% to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Distribution
Amlodipine
The volume of distribution is approximately 21L/kg. Approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Hydrochlorothiazide
Hydrochlorothiazide binds to albumin (40% to 70%) and distributes into erythrocytes. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

Metabolism
Amlodipine
Amlodipine is extensively metabolised by the liver to inactive metabolites.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by kidney.

Elimination
Amlodipine
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing.10% of the parent compound and 60% of amlodipine metabolites are excreted in the urine.

Hydrochlorothiazide
About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

Special Population
Geriatric Patients
Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

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% to 60%.

Renal Impairment
In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged.

THERAPEUTIC INDICATIONS
M-Low Plus (Amlodipine + Hydrochlorothiazide) is indicated for the treatment of hypertension & myocardial ischemia.

DOSAGE & ADMINISTRATION
Dosage may require modifications to adjust for individual sensitivities and associated medical conditions. The usual initial dose of M-low Plus (Amlodipine + Hydrochlorothiazide) Tablet is 5mg+12.5mg once daily. It may be increased to a maximum dose of 10mg+12.5mg depending on the individual patient's response or as directed by the physician.

ADVERSE REACTIONS
Following adverse reactions have been reported during treatment with Amlodipine and Hydrochlorothiazide combination:

Amlodipine
Somnolence, dizziness, headache (especially at the beginning of the treatment), palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema, fatigue, insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, paresthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, altered bowel habits (including diarrhea and constipation), dry mouth, alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema, arthralgia, myalgia, muscle cramps, back pain, micturition disorder, nocturia, increased urinary frequency, impotence, gynecomastia, chest pain, asthenia, malaise, weight increase, weight decrease and confusion.

Hydrochlorothiazide
Hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalances including hypochloremic alkalosis, hyponatremia, hypokalemia, hypomagnesemia, anorexia, gastric irritation, nausea, vomiting, constipation, diarrhea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, yellow vision, skin rashes, fever, pulmonary oedema, pneumonitis, anaphylaxis, toxic epidermal necrolysis, cholestatic, jaundice, pancreatitis, blood dyscrasias including thrombocytopenia and more rarely, granulocytopenia, leucopenia, aplastic anemia, hemolytic anemia and intestinal ulceration.

CONTRAINDICATIONS
Amlodipine + Hydrochlorothiazide combination is contraindicated in patients with:

- hypersensitivity to amlodipine, hydrochlorothiazide, dihydropyridine derivatives, other sulfonamide derived drugs, or any of the excipient of the product.
- severe hypotension.
- shock (including cardiogenic shock).
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- hemodynamically unstable heart failure after acute myocardial infarction.
- anuria.

PRECAUTIONS
Patients with Cardiac Failure
Amlodipine should be used with caution in patients with congestive heart failure, as it may increase the risk of future cardiovascular events & mortality.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle - closure glaucoma.

Diabetes and Hypoglycemia
Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.

Renal Disease
Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

Electrolyte and Fluid Balance Status
Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis and hypokalemia and hypomagnesemia.

Hyperuricemia
Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics.

Impaired Hepatic Function
This combination should be used with caution in patients with impaired hepatic function.

Parathyroid Disease
Calcium excretion is decreased by thiazide and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Mother
It is not known whether amlodipine is excreted in human milk but thiazides are excreted in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions
CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure.

CYP3A4 inducers
The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine.

Interaction with grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Verapamil & Dantrolene (infusion)
Due to risk of hyperkalemia, co-administration of amlodipine with Verapamil or Dentrolene be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Simvastatin
Co-administration of amlodipine results in the increase in simvastatin exposure.

Alcohol, barbiturates or narcotics
Hydrochlorothiazide in combination with alcohol, barbiturates or narcotics may cause potentiation of orthostatic hypotension.

Antidiabetic drugs
Dosage adjustment of the antidiabetic drug may be required, when given in combination with hydrochlorothiazide.

Cholestyramine and colestipol resins
Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.

Skeletal muscle relaxants
Hydrochlorothiazide increases responsiveness to the muscle relaxant. e.g.,Tubocurarine.

Lithium
Generally lithium should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity.

Non-steroidal anti-inflammatory drugs
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of hydrochlorothiazide.

Drug/Laboratory Test Interactions
Thiazides should be discontinued before carrying out tests for parathyroid function.

OVERDOSAGE
Amlodipine
Symptoms
Overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. The use of charcoal up to 2 hours after administration of amlodipine 10 mg reduce the absorption rate of amlodipine.

Hydrochlorothiazide
Symptoms
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

Treatment
In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
M-Low Plus (Amlodipine + Hydrochlorothiazide) Tablets 5mg+12.5mg are available in blister pack of 20's.
M-Low Plus (Amlodipine + Hydrochlorothiazide) Tablets 10mg+12.5mg are available in blister pack of 20's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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