For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Olmesartan Medoxomil and Amlodipine Besylate Tablets IP
(Brand Name: OLMEBLU™-AM Tablets)

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Olmesartan Medoxomil IP ……..…….… 20 mg.
Amlodipine Besylate IP equivalent to Amlodipine ……..... 5 mg.
Colours: Lake of Quinoline Yellow and Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Olmesartan medoxomil 20 mg and amlodipine 5 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

OLMEBLU-AM Tablets are indicated for the treatment of hypertension in adult patients whose blood pressure is not adequately controlled on olmesartan or amlodipine monotherapy.
If blood pressure is under control, there is reduction of risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
In stage 2 hypertension, OLMEBLU-AM Tablets can also be used as initial therapy.
OLMEBLU-AM Tablets may be administered alone, or with other antihypertensive agents.

4.2Posology and Method of Administration

For oral administration.
Adults: Recommended dose is 1 tablet to be administered once daily. If blood pressure is not adequately controlled after 2 weeks of therapy, dosage may be up titrated to 2 tablets once a day. Dosage must be individualized.

- Maximum recommended dose of olmesartan is 40 mg once daily.
- Maximum recommended dose of amlodipine is 10 mg once daily.

It is recommended that OLMEBLU-AM Tablets should be taken with or without food at the same time each day. The tablet should be swallowed with water.
Or, as prescribed by the physician.

4.3Contraindications

OLMEBLU-AM Tablets are contraindicated in the following:

- Hypersensitivity to olmesartan or to amlodipine or to any component of the formulation.
- Pregnancy.
- Severe hepatic impairment and biliary obstruction.
- Cardiogenic shock.
- Severe hypotension.
- Heart failure after acute myocardial infarction.
- Significant aortic stenosis.
- Acute porphyria.
- The concomitant use of olmesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4Special Warnings and Precautions for Use

Olmesartan

Morbidity in Infants: Children <1 year of age must not receive olmesartan for hypertension. Drugs that act directly on the RAAS can have effects on the development of immature kidneys.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated RAAS, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may be anticipated after initiation of treatment with olmesartan. Initiate treatment under close medical supervision. If hypotension occurs, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Impaired Renal Function: As a consequence of inhibiting the RAAS, changes in renal function may be anticipated in susceptible individuals treated with olmesartan. In patients whose renal function may depend upon the activity of the RAAS (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported.

Sprue-like Enteropathy: Severe chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with

olmesartan, exclude other etiologies. Consider discontinuation of olmesartan in cases where no other etiology is identified.

Hyperkalemia: Drugs that inhibit the RAAS, such as olmesartan, can cause hyperkalemia. Monitor serum electrolytes periodically. The risk, which may be fatal, is increased in elderly people, in patients with renal insufficiency, in diabetic patients, and in patients concomitantly treated with other drugs that may increase serum potassium levels.

Primary Aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the RAAS. Therefore, the use of olmesartan medoxomil is not recommended in such patients.

Amlodipine

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 amlodipine, particularly in patients with severe obstructive coronary artery disease.

Patients with Hepatic Failure: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function. Thus, caution should be exercised and dose should be titrated slowly in patients with severe hepatic impairment.

4.5Drug Interactions

The pharmacokinetics of amlodipine and olmesartan medoxomil is not altered when the drugs are co-administered. No drug interaction studies have been conducted with OLMEBLU-AM and other drugs. However, drug interaction studies have been conducted with the individual components of OLMEBLU-AM (olmesartan medoxomil and amlodipine). These are as follows:

Olmesartan

Cytochrome P450 Inducers/Inhibitors: Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes, thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

Antacids: The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3/Mg(OH)_2$].

Digoxin / Warfarin: No significant drug interactions were reported when olmesartan was co-administered with digoxin or warfarin.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including olmesartan medoxomil, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving olmesartan medoxomil and NSAID therapy. The

antihypertensive effect of angiotensin II receptor antagonists, including olmesartan medoxomil may be attenuated by NSAIDs including selective COX-2 inhibitors.

Dual Blockade of the RAAS: Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving a combination of two RAAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on olmesartan and other agents that affect the RAAS. Do not co-administer aliskiren with olmesartan in patients with diabetes. Avoid use of aliskiren with olmesartan in patients with renal impairment (GFR < 60 ml/min).

Colesevelam Hydrochloride: Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with ARBs, including olmesartan. Monitor serum lithium levels during concomitant use.

Potassium Supplements and Potassium Sparing Diuretics: Based on experience with the use of other drugs that affect the RAAS, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g., heparin) may lead to increases in serum potassium. Such concomitant use is therefore not recommended.

Effects on Ability to Drive and Use Machines: Olmesartan medoxomil has minor or moderate influence on the ability to drive and use machines. Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react.

<u>Amlodipine</u>

1. Impact of Other Drugs on Amlodipine

Sildenafil: Hypotensive effect is enhanced when amlodipine is given with sildenafil. Monitor for hypotension when these drugs are given together.

CYP3A Inhibitors (e.g., Ketoconazole, Itraconazole, Diltiazem, Erythromycin, Fluconazole, etc.): Co-administration with CYP3A inhibitors 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.

CYP3A Inducers (e.g., Carbamazepine, Phenytoin, Rifampin, etc.): No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure and edema should be closely monitored when amlodipine is co-administered with CYP3A inducers.

2. Impact of Amlodipine on Other Drugs

Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Thus, limit the dose of simvastatin to 20 mg once daily in patients on existing amlodipine therapy.

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of blood levels of cyclosporine and tacrolimus and dosage adjustment (whenever appropriate) is recommended.

4.6Use in Special Populations

Pregnant Women

Olmesartan: Pregnancy Category D; Amlodipine: Pregnancy Category C.

OLMEBLU-AM Tablets are contraindicated for use during pregnancy. Use of drugs that act on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity has been observed at high doses. As OLMEBLU-AM Tablet contains olmesartan which acts on RAAS, when pregnancy is detected or planned, discontinue its use as soon as possible.

Lactating Women

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted in low concentration in the milk of lactating rats. Limited available data from a published clinical study reports that amlodipine is present in human milk. However, no adverse effects of amlodipine on the breastfed infant have been observed. 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.

Paediatric Patients

Safety and efficacy of olmesartan with amlodipine combination therapy has not been established in paediatric patients. Thus, OLMEBLU-AM Tablets are not recommended for use in children.

Geriatric Patients

Elderly patients with normal renal and hepatic function may be given the same dose as recommended for adults. With olmesartan, no overall differences in effectiveness or safety were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC; therefore, caution should be exercised.

Renal Impairment Patients

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose. However, the maximum recommended dose of olmesartan in patients with mild to moderate renal impairment (creatinine clearance 20 to 60 ml/min) is 20 mg once daily. Due to lack of safety data, OLMEBLU-AM Tablets are not recommended in patients with severe renal impairment (creatinine clearance < 20 ml/min).

Hepatic Impairment Patients

For olmesartan, no dosage adjustment is required for patients with mild hepatic impairment. In patients with moderate hepatic impairment the maximum dose should not exceed 20 mg once daily. Amlodipine is extensively metabolized by the liver and the plasma elimination half-life increases in patients with impaired hepatic function. Also, 40 to 60% increase in AUC has been observed in patients with moderate to severe heart failure. Thus, slow dose titration and careful monitoring of blood pressure is advised in hepatically-impaired patients. There is no experience of olmesartan and amlodipine use in patients with severe hepatic impairment. Thus, OLMEBLU-AM Tablets are not recommended in this patient group. OLMEBLU-AM Tablets should not be used in patients with biliary obstruction.

4.7Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed with olmesartan medoxomil and amlodipine combination therapy. Both, olmesartan medoxomil and amlodipine can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. If patients taking this medicine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Thus, caution is recommended while driving a vehicle or operating machinery.

4.8Undesirable Effects

Olmesartan

Clinical Trials Experience

Olmesartan is generally well tolerated, with an incidence of adverse reactions similar to placebo. Adverse events are generally mild and transient in nature. The overall frequency of adverse reactions is not dose-related.

The following adverse reactions occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with olmesartan, but also occurred at about the same or greater incidence in patients receiving placebo: Back pain, bronchitis, increased creatinine phosphokinase, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis.

Other potentially important adverse reactions that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in controlled or open-label trials include:

Body as a Whole: Chest pain, peripheral edema.
Central and Peripheral Nervous System: Vertigo.
Gastrointestinal: Abdominal pain, dyspepsia, gastroenteritis, nausea.
Heart Rate and Rhythm Disorders: Tachycardia.
Metabolic and Nutritional Disorders: Hypercholesterolemia, hyperlipemia, hyperuricemia.
Musculoskeletal: Arthralgia, arthritis, myalgia.
Skin and Appendages: Rash, edema.
Laboratory Test Findings: Small decreases in hemoglobin and hematocrit; elevations of liver enzymes and/or serum bilirubin were observed infrequently.

Post-Marketing Experience
The following adverse reactions have been reported in post-marketing 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.
Body as a Whole: Asthenia, angioedema, anaphylactic reactions.
Gastrointestinal: Vomiting.
Metabolic and Nutritional Disorders: Hyperkalemia.
Musculoskeletal: Rhabdomyolysis, muscle spasm.
Urogenital System: Acute renal failure, increased blood creatinine levels.
Skin and Appendages: Alopecia, pruritus, urticaria.
Miscellaneous: Taste disorder.

Amlodipine
Most common adverse reactions reported with amlodipine are headache and pedal edema. Adverse effects with an incidence >1% in clinical studies included abdominal pain, nausea, dizziness, somnolence, flushing, palpitations, and fatigue.
Rare adverse events observed in controlled clinical trials or open trials or post-marketing surveillance studies (causal relationship is uncertain) included:
Cardiovascular: Arrthythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural hypotension, vasculitis, cardiac failure, pulse irregularity, extrasystoles.
Central and Peripheral Nervous System: Hypoesthesia, peripheral neuropathy, paresthesia, tremor, vertigo, ataxia, hypertonia, migraine, apathy, agitation, amnesia.
Gastrointestinal: Anorexia, constipation, dysphagia, diarrhea, flatulence, gastritis, increased appetite, loose stools, pancreatitis, vomiting, gingival hyperplasia/hypertrophy.
Musculoskeletal System: Arthralgia, arthrosis, muscle cramps, myalgia, muscle weakness, twitching.
Psychiatric: Sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: Dyspnea, epistaxis, cough, rhinitis.

Skin and Appendages: Rash, pruritus, urticaria, angioedema, skin dryness, alopecia, skin discoloration.
Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, abnormal visual accommodation, xerophthalmia, tinnitus, parosmia, taste perversion.
Urinary System: Increased micturition frequency, nocturia, dysuria, polyuria.
Autonomic Nervous System: Dry mouth, increased sweating, cold and clammy skin.
Metabolic and Nutritional: Hyperglycemia, thirst.
Hemopoietic: Leukopenia, purpura, thrombocytopenia.
General: Allergic reaction, back pain, hot flushes, malaise, pain, rigors, weight gain, weight loss.

4.9Overdose

Olmesartan

Limited data are available with regards to overdose of olmesartan in humans. The most likely manifestations of overdose would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension occurs, supportive treatment should be initiated. No information is available regarding the dialysability of olmesartan.

Amlodipine

Overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose of amlodipine 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 amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

5. Pharmacological Properties

5.1 Mechanism of Action

Olmesartan

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the RAAS, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT2 receptor is also found in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

Amlodipine

Amlodipine is a dihydropyridine class of long-acting calcium channel blocker – CCB (calcium antagonist). Amlodipine inhibits the transmembrane influx of calcium ions (Ca^{++}) 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. Serum calcium concentration is not affected by amlodipine.
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.

5.2Pharmacodynamic Properties

Olmesartan

Olmesartan is an angiotensin II receptor blocker (ARB), also called as sartan, class of antihypertensive drugs. In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, tachyphylaxis during long-term treatment, or rebound hypertension after cessation of therapy. Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval.
Olmesartan medoxomil doses of 2.5 mg to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of >40 mg giving >90% inhibition at 24 hours.
Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan had minimal influence on aldosterone levels and no effect on serum potassium.

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. These

decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

5.3Pharmacokinetic Properties

Olmesartan

Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

Absorption: Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

Distribution: The volume of distribution of olmesartan is approximately 17 litres. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells.

Metabolism and Excretion: Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours.

Amlodipine

Absorption: After oral administration of therapeutic doses, amlodipine produces peak plasma concentrations between 6 to 12 hours. Absolute bioavailability has been estimated to be between 64 to 90%. The bioavailability is not altered by the presence of food.

Distribution: The volume of distribution is approximately 21 l/kg. *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: Excretion from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

6. Nonclinical Properties

6.1 Animal Toxicology

Olmesartan

Toxicity: In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT1 receptors); reduction in heart weight; a reduction of red cell parameters (erythrocytes, haemoglobin,

haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of olmesartan medoxomil have also occurred in preclinical trials on other AT1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

Carcinogenesis: Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Mutagenesis: Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Impairment of Fertility: Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

Teratogenicity: No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose (MRHD) on a mg/m^2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricula, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses ≥ 8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

Amlodipine

Carcinogenesis: 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.

Mutagenesis: Mutagenicity studies conducted with amlodipine revealed no drug related effects at either the gene or chromosome level.

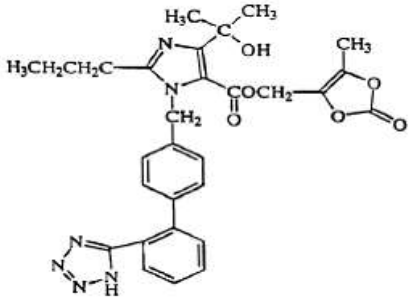
Impairment of Fertility: There was no effect on the fertility of rats treated orally with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [based on body weight of 50 kg] the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).
Teratogenicity: 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 maximum recommended human dose 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.

7. Description

OLMEBLU-AM Tablets are yellow coloured, circular, biconvex, scored on one side and plain on other side, film coated tablets.
OLMEBLU-AM Tablets contains 20 mg of olmesartan medoxomil and 5 mg of amlodipine for oral administration in adults.

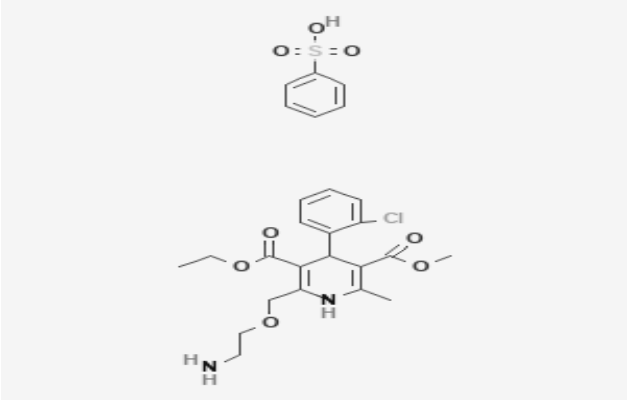
Olmesartan Medoxomil

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist used for the management of hypertension.
Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder.
Molecular Weight: 558.59 g/mol.
Molecular Formula: C29H30N6O6.
Chemical Name: 2,3-dihydroxy-2-butenyl 4-(1 hydroxy-1- methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5 carboxylate, cyclic 2,3- carbonate.
Structural Formula:



Amlodipine Besylate

Amlodipine Besylate is the besylate salt of amlodipine. Amlodipine is a long-acting calcium channel blocker (CCB) of a synthetic dihydropyridine class with antihypertensive and antianginal effects.
Amlodipine besylate is a white crystalline powder.
Molecular Weight: 567.1 g/mol.
Molecular Formula: C20H25CIN2O5•C6H6O3S.
Chemical Name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.
Structural Formula:



Inactive ingredients (excipients) of OLMEBLU-AM Tablets contain Croscarmellose Sodium, Avicel PH 101, Colloidal Silicon Dioxide, Talcum, Magnesium Stearate, Starch, and Blackberry Flavour Colorezy Yellow.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting doctor.
- Patients are advised to take OLMEBLU-AM Tablets once a day, with or without food. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose at a time.
- If patients miss a dose, they can take it as soon as they remember. Do not take this medicine if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- Pregnant women should strictly avoid use of this medicine. When pregnancy is detected or planned, discontinue OLMEBLU-AM Tablets as soon as possible.
- Advise nursing mothers not to breastfeed their infants during treatment with OLMEBLU-AM Tablets.
- Use of this medicine is not recommended in children.
- Advise patients to avoid driving vehicle or operating machinery or engaging in other tasks requiring mental alertness until the patient's response to therapy has been determined.
- Patients should be informed that while taking OLMEBLU-AM Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting their doctor.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A Subsidiary of Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No.: 31/UA/2013; Date of Product Permission: 14/05/2024.

12. Date of Revision

May 2024.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.