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 Tablets IP 20 mg/40 mg
(Brand Name: Olmeblu™ 20 mg / 40 mg Tablets)

2. Qualitative and Quantitative Composition

Olmeblu 20 mg
Each film coated tablet contains:
Olmesartan Medoxomil IP …… 20 mg
Excipients …….. q.s.
Colours: Lake of Tartrazine and Titanium Dioxide IP.

Olmeblu 40 mg
Each film coated tablet contains:
Olmesartan Medoxomil IP …… 20 mg
Excipients …….. q.s.
Colours: Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Olmesartan medoxomil 20 mg and 40 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

OLMEBLU Tablets are indicated for the treatment of essential hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
OLMEBLU Tablets may be used alone, or in combination with other antihypertensive drugs.

4.2Posology and Method of Administration

For oral administration.
Adults: Olmesartan is effective in doses between 20 mg to 40 mg once daily. The usual recommended starting dose of olmesartan is 20 mg once daily when used as monotherapy in patients who are not volume-depleted. For patients requiring further reduction in blood pressure

after 2 weeks of therapy, the dose may be increased to 40 mg once daily. The antihypertensive effect of olmesartan is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy.
Dosage must be individualized. It is recommended that OLMEBLU Tablets be taken at about the same time each day, with or without food. The tablet should be swallowed and not to be chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

OLMEBLU Tablets are contraindicated in the following:

- In patients with hypersensitivity to olmesartan or to any component of the formulation.
- Pregnancy.
- Biliary obstruction.
- 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

Morbidity in Infants: Children <1 year of age must not receive olmesartan for hypertension. Drugs that act directly on the renin angiotensin aldosterone system (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.

4.5Drug Interactions

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.

4.6Use in Special Populations

Pregnant Women

Olmesartan medoxomil - Pregnancy Category D. OLMEBLU 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. When pregnancy is detected or planned, discontinue use of OLMEBLU Tablets 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. 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

The safety and efficacy of olmesartan in children below 6 years of age has not been established. Olmesartan (10 to 20 mg per day) can be used in children between 6 to 18 years of age. OLMEBLU Tablets are not intended for use in children due to its higher dosage strength. If required, children above 6 years can use paediatric formulations of lower dosage strength.

Geriatric Patients

No overall differences in effectiveness or safety have been observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No adjustment of dosage is generally required in elderly people with normal renal function. If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored.

Renal Impairment Patients

The maximum 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, use of olmesartan in patients with severe renal impairment (creatinine clearance < 20 ml/min) is not recommended.

Hepatic Impairment Patients

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. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan use in patients with severe hepatic impairment, therefore use is not recommended in this patient group. Olmesartan should not be used in patients with biliary obstruction.

4.7Effect on Ability to Drive and Use Machines

Olmesartan has minor or moderate influence on the ability to drive and use machines. Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy, including olmesartan, which may impair patient's ability to react. Thus, caution is recommended while driving a vehicle or operating machinery.

4.8Undesirable Effects

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.
Urogenital System: Acute renal failure, increased blood creatinine levels.
Skin and Appendages: Alopecia, pruritus, urticaria.

4.9Overdose

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.

5. Pharmacological Properties

5.1 Mechanism of Action

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.

5.2Pharmacodynamic Properties

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.

5.3Pharmacokinetic Properties

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.

6. Nonclinical Properties

6.1 Animal Toxicology

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.

7. Description

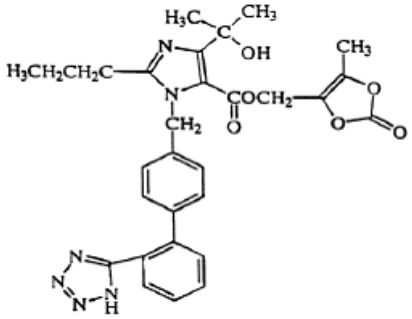
OLMEBLU 20 Tablets are yellow coloured, round, biconvex, scored on one side, film coated tablets.

OLMEBLU 40 Tablets are white coloured, round, biconvex, scored on one side, film coated tablets.

OLMEBLU 20 Tablets contains 20 mg of olmesartan medoxomil whereas OLMEBLU 40 Tablet contains 40 mg of olmesartan medoxomil for oral administration in adults.

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: $C_{29}H_{30}N_6O_6$.

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:



Inactive ingredients (excipients) of OLMEBLU 20 Tablets contain Lactose, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Purified Water, Colloidal Silicon Dioxide, Talcum, Magnesium Stearate, and Blackberry Fla. Colorezy Yellow.

Inactive ingredients (excipients) of OLMEBLU 40 Tablets contain Lactose, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Purified Water, Colloidal Silicon Dioxide, Talcum, Magnesium Stearate, and Blackberry Fla. Colorezy White.

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 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 therapy as soon as possible.
- Advise nursing women not to breastfeed during treatment with OLMEBLU Tablets.
- Advice patients not to use potassium supplements or salt substitutes that contain potassium without consulting their healthcare provider because of risk of hyperkalemia (increased potassium level in the blood).
- Patients should be informed that while taking OLMEBLU 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

OLMEBLU-20: Mfg. Lic. No.: 31/UA/2013; Date of FDA Product Permission: 31/01/2014.
OLMEBLU-40: Mfg. Lic. No.: 31/UA/2013; Date of FDA Product Permission: 31/01/2014.

12. Date of Revision

April 2021.

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.