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 Hydrochlorothiazide Tablets IP
(Brand Name: OLMEBLU™-H 20 / OLMEBLU™-H 40 Tablets)

2. Qualitative and Quantitative Composition

OLMEBLU-H 20 Tablets
Each film coated tablet contains:
Olmesartan Medoxomil IP ……. 20 mg
Hydrochlorothiazide IP ……..... 12.5 mg
Excipients …… q.s.
Colour: Titanium Dioxide IP.

OLMEBLU-H 40 Tablets
Each film coated tablet contains:
Olmesartan Medoxomil IP ……. 40 mg.
Hydrochlorothiazide IP ……..... 12.5 mg
Excipients …… q.s.
Colours: Lake of Quinoline Yellow and Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Olmesartan medoxomil 20 mg / 40 mg and hydrochlorothiazide 12.5 mg / 12.5 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

OLMEBLU-H Tablets are indicated for the treatment of hypertension when monotherapy with olmesartan is inadequate to achieve the desired blood pressure goal.
In stage 2 hypertension, OLMEBLU-H Tablets can be used as initial therapy.
OLMEBLU-H Tablets may be used alone, or in combination with other antihypertensive drugs.

4.2Posology and Method of Administration

For oral administration.

Adults: Recommended starting dose is 1 OLMEBLU-H 20 Tablet (20/12.5 mg of olmesartan/hydrochlorothiazide) to be administered once daily.
If blood pressure is not adequately controlled after 2 to 4 weeks of therapy, dose may be increased to 1 OLMEBLU-H 40 Tablet (40/12.5 mg of olmesartan/hydrochlorothiazide) to be administered once daily. Dosage must be individualized.

- Olmesartan is effective in doses between 10 mg to 40 mg once daily.
- Hydrochlorothiazide is effective in doses between 12.5 mg to 50 mg once daily.

It is recommended that OLMEBLU-H Tablets should be taken with or without food at the same time each day. The tablet should be swallowed and not to be chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

OLMEBLU-H Tablets are contraindicated in the following:

- In patients with hypersensitivity to olmesartan or to hydrochlorothiazide or to any component of the formulation.
- Pregnancy.
- Refractory hyponatraemia.
- Symptomatic hyperuricaemia/gout.
- Severe hepatic impairment, cholestasis, and biliary obstructive disorders.
- Severe renal impairment.
- In patients with anuria.
- 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

Fetal Toxicity: 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 and death. 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, discontinue OLMEBLU-H Tablets as soon as possible. Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia.
Morbidity in Infants: Children less than 1 year of age must not receive olmesartan-containing preparations 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- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with OLMEBLU-H Tablets. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given

an intravenous infusion of normal saline. When electrolyte and fluid imbalances have been corrected, OLMEBLU-H Tablets usually can be continued without difficulty. A transient hypotensive response is not a contraindication to further treatment.

Impaired Renal Function: Changes in renal function including acute renal failure can be caused by drugs that inhibit the RAAS and by diuretics. Patients whose renal function may depend in part on the activity of the RAAS (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure with OLMEBLU-H Tablets. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function with OLMEBLU-H Tablets.

Hypersensitivity Reactions: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Electrolyte and Metabolic Imbalances:

1. **Potassium, Sodium, and Magnesium (Electrolytes):** OLMEBLU-H Tablets contain hydrochlorothiazide which can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. OLMEBLU-H Tablets also contain olmesartan. 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.
2. **Lipids:** Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.
3. **Uric Acid:** Hyperuricemia may occur or frank gout may be precipitated in patients receiving thiazide therapy.
4. **Calcium:** Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor serum calcium levels.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

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 OLMEBLU-H Tablets in cases where no other etiology is identified.

Primary Aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive drugs which act by inhibition of the RAAS. Therefore, the use of OLMEBLU-H Tablets is not recommended in such patients.

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

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

4.5Drug Interactions

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 angiotensin receptor blockers (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, angiotensin converting enzyme (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.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive antihypertensive effect may occur, thus, reduction in dosage is required.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 %, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines, but not sufficient to preclude their use.

Skeletal Muscle Relaxants (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxants such as curare derivatives.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In some patients, administration of NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Digoxin: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

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

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

4.6Use in Special Populations

Pregnant Women

Olmesartan medoxomil: Pregnancy Category D; Hydrochlorothiazide: Pregnancy Category B. OLMEBLU-H 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, and death. 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. Also, the routine use of diuretics exposes mother and fetus to unnecessary hazard. Thus, when pregnancy is detected or planned, discontinue OLMEBLU-H Tablets as soon as possible.

Lactating Women

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Thiazides appear 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 OLMEBLU-H Tablets, taking into account the importance of the drug to the mother.

Paediatric Patients

The safety and effectiveness of OLMEBLU-H Tablets in paediatric patients have not been established. Thus, OLMEBLU-H Tablets are not recommended for use in children.

Geriatric Patients

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 diseases and/or other drug therapy. Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to OLMEBLU-H Tablets may be greater in elderly patients with impaired renal function.

Renal Impairment Patients

No dose adjustment is required in patients with mild (creatinine clearance 60 to 90 ml/min) or moderate (creatinine clearance 30 to 60 ml/min) renal impairment. Safety and effectiveness of OLMEBLU-H Tablets in patients with severe renal impairment (creatinine clearance $\leq$ 30 ml/min) have not been established. OLMEBLU-H Tablets are contraindicated in patients with severe renal impairment.

Hepatic Impairment Patients

For olmesartan, no dosage adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, the maximum dose of olmesartan should not exceed 20 mg once daily. There is no experience of olmesartan in patients with severe hepatic impairment. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are receiving diuretics and/or other antihypertensive agents. With hydrochlorothiazide, minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

OLMEBLU-H Tablets should be used with caution in patients with mild to moderate hepatic impairment. OLMEBLU-H Tablets should not be used in patients with severe hepatic impairment, cholestasis, and 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 hydrochlorothiazide combination therapy. Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy which may impair patient's ability to react. Both, olmesartan and hydrochlorothiazide can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. 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.

Urogenital System: Acute renal failure, increased blood creatinine levels.

Skin and Appendages: Alopecia, pruritus, urticaria.

Hydrochlorothiazide

Adverse events that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: Weakness.

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

Metabolic: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Restlessness.

Renal: Renal dysfunction, interstitial nephritis, renal failure.

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis (including toxic epidermal necrolysis).

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

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.

Hydrochlorothiazide

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.

In the event of overdose, 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. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

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.

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a thiazide class of diuretic drugs which blocks the reabsorption of sodium (Na^+) and chloride (Cl^-) ions, and it thereby increases the quantity of sodium traversing the distal tubule of nephron. By this mechanism, hydrochlorothiazide increases excretion of water (diuretic effect), reduces blood volume, and thereby decreases cardiac output. These effects help to reduce increased blood pressure. As hydrochlorothiazide has weak antihypertensive effect, it is usually combined with other antihypertensive drugs.

A portion of the additional sodium presented to the distal tubule of nephron is exchanged there for potassium (K^+) and hydrogen (H^+) ions. With continued use of hydrochlorothiazide and depletion

of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen, and chloride ions (electrolyte imbalance). Hydrochlorothiazide also decreases the excretion of calcium (Ca^{++}) and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate.

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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide class of diuretic agent. Hydrochlorothiazide is widely used to treat hypertension and edema. Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased.

Thiazides do not affect normal blood pressure. Peak effect of hydrochlorothiazide is observed at about 4 hours of dosing and activity persists for up to 24 hours.

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.

Hydrochlorothiazide
Absorption: Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/ml following oral doses of 12.5 to 100 mg.
Distribution: Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Plasma protein binding is approximately 40% to 68%.
Metabolism and Excretion: The plasma elimination half-life is 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentration of hydrochlorothiazide is increased and the elimination half-life is prolonged.

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.

Hydrochlorothiazide

Carcinogenesis: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Mutagenesis: Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Impairment of Fertility: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Teratogenicity: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

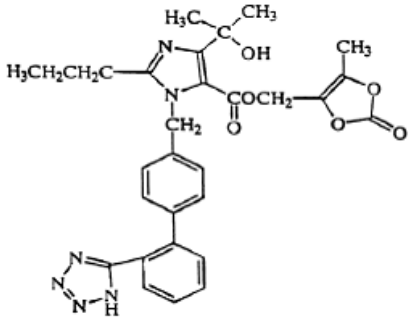
7. Description

OLMEBLU-H 20 Tablets are white coloured, circular, biconvex, scored line on one side and plain on the other side, film coated tablets.
OLMEBLU-H 40 Tablets are yellow coloured, circular, biconvex, scored line on one side and plain on other side, film coated tablets.

OLMEBLU-H 20 Tablets contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide for oral administration in adults.
OLMEBLU-H 40 Tablets contains 40 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide for oral administration in adults.

Olmesartan medoxomil

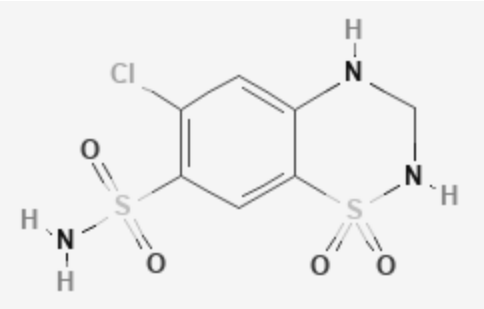
Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist used for the management of hypertension.
Olmesartan medoxomil is a white to light yellowish-white powder or crystalline 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:



Hydrochlorothiazide

Hydrochlorothiazide is short acting thiazide class of diuretic used for the treatment of hypertension and congestive heart failure.
Hydrochlorothiazide is a white or practically white crystalline powder.
Molecular Weight: 297.7 g/mol.

Molecular Formula: C7H8ClN3O4S2.
Chemical Name: 6-chloro-1,1-dioxo-3,4-dihydro-2H-1λ6,2,4-benzothiadiazine-7-sulfonamide.
Structural Formula:



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

Inactive ingredients (excipients) of OLMEBLU-H 40 Tablets contain Lactose, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Purified Water, Colloidal Silicon Dioxide, Talcum, Magnesium Stearate, and Blackberry Fla. 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-H 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-H Tablets as soon as possible.
- Advise nursing mothers not to breastfeed their infants during treatment with OLMEBLU-H Tablets.
- Use of this medicine is not recommended in children.
- Patients should be informed that while taking OLMEBLU-H Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting to 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-H 20: Mfg. Lic. No.: 31/UA/2013; Date of FDA Product Permission: 31/01/2014.
OLMEBLU-H 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.