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

OLSAR – H

1. **Generic Name**

Olmesartan Medoxomil and Hydrochlorothiazide Tablets I.P

2. . Qualitative and quantitative composition

OLSAR - H 20

Each film coated tablet contains:

Olmesartan Medoxomil I.P.…….20mg

Hydrochlorothiazide I.P. ……12.5mg

Excipients……q.s.

Colours: Ferric Oxide Yellow USPNF & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Yellow.

OLSAR - H 40

Each film coated tablet contains:

Olmesartan Medoxomil I.P. ……..40mg

Hydrochlorothiazide I.P. ……12.5mg

Excipients…… q.s.

Colours: Ferric Oxide Red USPNF & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Red.

3. Dosage form and strength

Dosage form: Film Coated tablet

Strength: Olmesartan Medoxomil I.P. 20mg, 40 mg and Hydrochlorothiazide I.P. 12.5mg

4. . Clinical particulars

4.1 Therapeutic indication

For treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Dosage: As directed by the Physician

4.3 Contraindications

Olmesartan Medoxomil

Hypersensitivity to the active substance or to any of the excipients.

Second and third trimesters of pregnancy.

Biliary obstruction

The concomitant use of Olmesartan Tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

Hydrochlorothiazide

Anuria. Hypersensitivity to this product or to other sulfonamide-derived drugs.

4.4 Special warnings and precautions for use

Olmesartan Medoxomil

Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Such conditions should be corrected before the administration of olmesartan medoxomil.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation

When olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of olmesartan medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 ml/min) (see sections 4.2 and 5.2). There is no experience of the administration of olmesartan medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance < 12 ml/min).

Hepatic impairment

There is no experience in patients with severe hepatic impairment and therefore use of olmesartan medoxomil in this patient group is not recommended (see section 4.2 for dosage recommendations in patients with mild or moderate hepatic impairment).

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

The risk, that may be fatal, is increased in elderly, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered. (see also below section “Dual blockade of the renin-angiotensin-aldosterone system (RAAS)”).

The main risk factors for hyperkalaemia to be considered are:

- Diabetes, renal impairment, age (> 70 years)

- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), and heparin, Immunosuppresors as ciclosporin or tacrolimus, trimethoprim

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extended trauma).

Close-monitoring of serum potassium in at risk patients is recommended (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Lithium

As with other angiotensin-II receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended (see section 4.5).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of olmesartan medoxomil is not recommended in such patients.

Sprue-like enteropathy

In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, and in the absence of other apparent etiologies, olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.

Ethnic differences

As with all other angiotensin II antagonists, the blood pressure lowering effect of olmesartan medoxomil is somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

Pregnancy

Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonist's therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other

As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Hydrochlorthiazide

WARNINGS: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Thiazides may add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics (see PRECAUTIONS: Drug Interactions).

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.

PRECAUTIONS: General: All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life

threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patient's dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyper glycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

4.5 Drug-Interaction

Olmesartan Medoxomil

Interaction studies have only been performed in adults.

Effects of other medicinal products on olmesartan medoxomil

Other antihypertensive medications:

The blood pressure lowering effect of olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.

ACE-inhibitors, angiotensin II receptor blockers or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4).

Potassium supplements and potassium sparing diuretics:

Based on experience with the use of other drugs that affect the renin-angiotensin system, 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 (see section 4.4). Such concomitant use is therefore not recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses> 3 g/day and also COX-2 inhibitors) and angiotensin II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

Bile acid sequestering agent colesevelam

Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces t1/2. Administration of olmesartan medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering olmesartan medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered.

Other compounds:

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Coadministration of warfarin and digoxin had no effect on the pharmacokinetics of olmesartan.

Effects of olmesartan medoxomil on other medicinal products:

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore, use of olmesartan medoxomil and lithium in combination is not recommended (see section 4.4). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other compounds:

Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminium hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular olmesartan medoxomil had no

significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Olmesartan had no clinically relevant inhibitory effects on *in vitro* human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal inducing effects on rat cytochrome P450 activities. Therefore, *in vivo* interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

Paediatric population:

Interaction studies have only been performed in adults. It is not known if the interactions in children are similar to those in adults.

Hydrochlorthiazide

Drug Interactions: When given 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 effect or potentiation. 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 the 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, Nondepolarizing (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxant. Lithium: Generally, should not be given with diuretics.

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide. Non-Steroidal Anti-Inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Therefore,when hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS: General). Carcinogenesis, Mutagenesis, Impairment of Fertility: 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 up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. 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. 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.

4.6 **Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Olmesartan Medoxomil

Pregnancy

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II antagonists is contraindicated during the second and third trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-

hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Angiotensin II antagonists therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II antagonists should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breastfeeding

Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Because no information is available regarding the use of Olmesartan Tablets during breast-feeding, Olmesartan Tablets is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide

Pregnancy: Teratogenic Effects. Pregnancy Category B: 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. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects:

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use: There are no well controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients. (See DOSAGE AND ADMINISTRATION: Infants and Children.)

4.7 Effects on ability to drive and use machines

Olmesartan Tablets 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.

HYDROCHLORTHIAZIDE

Not available

4.8 Undesirable effects

Olmesartan Medoxomil

Summary of the safety profile

The most commonly reported adverse reactions during treatment with olmesartan are headache (7.7%), influenza-like symptoms (4.0%) and dizziness (3.7%).

In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on olmesartan medoxomil and 0.9% on placebo).

The incidence was also somewhat higher on olmesartan medoxomil compared with placebo for hypertriglyceridaemia (2.0% versus 1.1%) and for raised creatine phosphokinase (1.3% versus 0.7%).

Tabulated list of adverse reactions

Adverse reactions from olmesartan in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized in the below table.

The following terminologies have been used in order to classify the occurrence of adverse reactions very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Class	Adverse Reactions	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon

Immune system disorders	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
Nervous system disorders	Dizziness	Common
	Headache	Common
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	Common
	Pharyngitis	Common
	Cough	Common
	Rhinitis	Common
Gastrointestinal disorders	Gastroenteritis	Common
	Diarrhoea	Common
	Abdominal pain	Common
	Nausea	Common
	Dyspepsia	Common
	Vomiting	Uncommon
	Sprue-like enteropathy (see section 4.4)	Very rare
Skin and subcutaneous tissue disorders	Exanthema	Uncommon
	Allergic dermatitis	Uncommon
	Urticaria	Uncommon
	Rash	Uncommon
	Pruritus	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Arthritis	Common
	Back pain	Common
	Skeletal pain	Common
	Myalgia	Uncommon
	Muscle spasm	Rare
Renal and urinary disorders	Haematuria	Common

	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
General disorders and administration site conditions	Pain	Common
	Chest pain	Common
	Peripheral oedema	Common
	Influenza-like symptoms	Common
	Fatigue	Common
	Face oedema	Uncommon
	Asthenia	Uncommon
	Malaise	Uncommon
	Lethargy	Rare
Investigations	Hepatic enzymes increased	Common
	Blood urea increased	Common
	Blood creatine phosphokinase increased	Common
	Blood creatinine increased	Rare

Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers.

Additional information on special populations

Paediatric population:

The safety of olmesartan was monitored in 361 children and adolescents, aged 1-17 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Epistaxis is a common adverse event in children (i.e. ≥ 1/100 to < 1/10) that has not been reported in adults.

- During the 3 weeks of double blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6-17 years of age in the high olmesartan dose group.

The overall safety profile for olmesartan in paediatric patients does not differ significantly from the safety profile in adults.

Elderly (age 65 years or over):

In elderly people the frequency of hypotension is slightly increased from rare to uncommon.

HYDROCHLORTHIAZIDE

The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity. Body as a Whole: Weakness. Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs). Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia. Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura**.**

Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia. **Musculoskeletal:** Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness**.**

Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS).

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

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

4.9 Overdose

Olmesartan Medoxomil

Only limited information is available regarding overdosage in humans. The most likely effect of overdosage is hypotension. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive. No information is available regarding the dialysability of olmesartan.

HYDROCHLORTHIAZIDE

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 overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

5. 5. Pharmacological properties

5.1 Mechanism of Action

Olmesartan Medoxomil

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT_1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT_1) receptor.

Hydrochlorthiazide

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen 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. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

5.2 **Pharmacodynamicproperties**

Olmesartan Medoxomil

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT_1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT_1) receptor.

Hydrochlorthiazide

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. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

5.3 Pharmacokinetic properties

Olmesartan Medoxomil

Absorption and distribution

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract.

No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6 %.

The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7 %), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound coadministered drugs is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 - 29 L).

Biotransformation and elimination

Total plasma clearance was typically 1.3 L/h (CV, 19 %) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10 - 16 % of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6 %, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40 %) and hepato-biliary excretion (ca 60 %). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

The terminal elimination half-life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 - 0.7 L/h and was independent of dose.

Pharmacokinetics in special populations:

Paediatric population

The pharmacokinetics of olmesartan was studied in paediatric hypertensive patients aged 1 to16 years. The clearance of olmesartan in paediatric patients was similar to that in adult patients when adjusted by the body weight.

There is no pharmacokinetic information available in renally impaired paediatric subjects.

Elderly people (age 65 years or older)

In hypertensive patients, the AUC at steady state was increased by ca 35 % in elderly patients (65 - 75 years old) and by ca 44 % in very elderly patients (≥75 years old) compared with the younger age group. This may be at least in part related to a mean decrease in renal function in this group of patients.

Renal impairment

In renally impaired patients, the AUC at steady state increased by 62 %, 82 % and 179 % in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2, 4.4).

Hepatic impairment

After single oral administration, olmesartan AUC values were 6 % and 65 % higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26 %, 0.34 % and 0.41 %, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC was again about 65 % higher than in matched healthy controls. Olmesartan mean C_{max} values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2, 4.4).

Drug interactions

Bile acid sequestering agent colesevelam

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half-life of olmesartan was reduced by 50-52% irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride

Hydrochlorthiazide

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. 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. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Primarily renal pathways eliminate hydrochlorothiazide. 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 concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged. When Hydrochlorothiazide is administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.

6. Nonclinical properties

6.1 Animal Toxicology

Olmesartan Medoxomil

In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT_1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT_1receptors); 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 AT_1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE inhibitors and other AT_1 receptor antagonists, would appear to have no clinical relevance.

Like other AT_1 receptor antagonists olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures *in vitro*. No relevant effects were observed in several *in vivo* studies using olmesartan medoxomil at very high oral doses of up to 2000 mg/kg. The overall data of a comprehensive genotoxicity testing suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan medoxomil was not carcinogenic, neither in rats in a 2-year study nor in mice when tested in two 6-month carcinogenicity studies using transgenic models.

In reproductive studies in rats, olmesartan medoxomil did not affect fertility and there was no evidence of a teratogenic effect. In common with other angiotensin II antagonists, survival of offspring was reduced following exposure to olmesartan medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats, however, there was no indication of a foetotoxic effect.

Hydrochlorthiazide

Toxicity

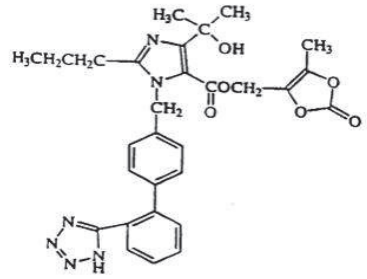
Recognized side effects that have been associated with the use of hydrochlorothiazide include hypokalemia with resultant muscle cramps, cardiac arrhythmia, hyperglycemia, and hyperlipidemia. A variety of hypersensitivity reactions have also been reported. Electrolyte imbalances, in particular hypokalemia and hypomagnesemia, may be involved in increased incidences of sudden death in patients with pre-existing electrocardiographic abnormalities. Results of the large Multiple Risk Factor Intervention Trial, a 10-year, multicenter study of factors involved in heart disease, indicated that high dose hydrochlorothiazide therapy (100 mg/day) was associated with greater incidences of sudden death in patients with both high blood pressure and electrocardiographic abnormalities. The involvement of hypokalemia and hypomagnesemia in this observation remains a point of controversy. One electrolyte change that occurs with long-term hydrochlorothiazide therapy in humans is increased calcium ion retention; hypercalcemia occasionally results. A related finding is an association of hydrochlorothiazide treatment with hyperparathyroidism. It has been suggested that thiazides cause a primary hyperparathyroidism, and the reduced calcium ion excretion and increased potassium ion loss seen with these diuretics may, at least in part, be secondary to increased parathyroid hormone secretion. gave 20

dogs daily doses of 50-200 mg hydrochlorothiazide for up to 9 months; all dogs administered hydrochlorothiazide had enlarged and hyperactive parathyroid glands. Thiazide diuretics also induce a transient increase in serum cholesterol and triglyceride levels, raising the possibility that long-term treatment may contribute to atherosclerosis, although the importance of these transient increases has been disputed. Hypertensive individuals receiving 50 mg hydrochlorothiazide per day for 4 weeks had increased concentrations of total plasma cholesterol, of high density, low density, and very low density lipoproteins, and of triglycerides. Increased plasma levels of fasting glucose and insulin were also observed dosed Syrian golden hamsters daily with 1,2, or 4 mg/kg hydrochlorothiazide by gavage for 6 months. At 6 months, they observed increased total cholesterol, triglyceride, and high density lipoprotein cholesterol levels. glucose intolerance is a frequently encountered side effect of long-term thiazide therapy and may be associated with hypokalemia, but the mechanism for this effect is not understood. Other diuretics have similar effects on glucose tolerance. Immunologic reactions to hydrochlorothiazide therapy were reported, including cases of severe allergic pneumonitis, a photo allergic dermatitis resembling subacute cutaneous lupus erythematosus and several types of hematologic dyscrasias. Neutropenia was reported in several patients with a pattern of onset which suggested a toxic depression of the bone marrow. On the other hand, thrombocytopenia also was reported with hydrochlorothiazide therapy and with other thiazides and appears to be immunologically mediated. In one person, a specific IgM antibody was identified as an antiplatelet factor associated with hydrochlorothiazide-induced thrombocytopenia. The LO50 of orally administered hydrochlorothiazide to an unspecified strain of mice was 3,080 mg/kg. fed diets containing 0 or 1,000 ppm hydrochlorothiazide to groups of 24 male and 24 female rats for 2 years. The incidence and severity of chronic progressive nephropathy was increased in the dosed rats, as were lesions secondary to chronic renal disease and polyarthritis and mural thrombosis. No increases in neoplastic lesions were seen in dosed rats.

7. . Description

Olmesartan Medoxomil

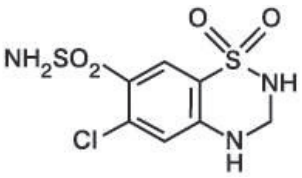
Olmesartan Medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan medoxomil is chemically described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is $C_{29}H_{30}N_6O_6$ and molecular weight is 558.6. The structural formula for olmesartan medoxomil is:



Olmesartan Medoxomil is a white or almost white crystalline powder which is slightly soluble in ethanol 95% and practically insoluble in heptane and water.

Hydrochlorothiazide

Hydrochlorothiazide is a white or almost white, crystalline powder; odourless with a molecular weight of 297.74. It is soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



OLSAR – H 20

Olmesartan Medoxomil and Hydrochlorothiazide tablets are light to dark yellow coloured, round biconvex film coated tablet plain on both sides. The excipients used are Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Yellow.

OLSAR – H 40

Olmesartan Medoxomil and Hydrochlorothiazide tablets are light to dark brick red coloured, round, biconvex film coated tablet with score line on one side and plain on other side. The excipients used are

Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Red.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

OLSAR – H is available in blister strip of 10 tablets each.

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light & moisture. Keep all medicines out of reach of children.

9. Patient Counselling Information

OLSAR - H

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or your pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What OLSAR - H is and what it is used for

OLSAR H is combination of the active substance Olmesartan and Hydrochlorothiazide belongs to a group of medications known as thiazide diuretics; it is a medication which causes increased volume of urine. It is only available with a doctor's prescription.

Olmesartan Tablets belong to a group of medicines called angiotensin-II receptor antagonists. They lower blood pressure by relaxing the blood vessels.

9.2 What you need to know before you take OLSAR H

Do not take OLSAR H

Tablets:

• if you are allergic to **OLSAR H** or any of the other ingredients of this medicine

• if you are more than 3 months pregnant. (It is also better to avoid Olmesartan Tablets in early pregnancy - see pregnancy section).

• if you suffer from yellowing of the skin and eyes (jaundice) or problems with drainage of the bile from the gallbladder (biliary obstruction e.g. gallstones).

• if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking **OLSAR H**.

Tell your doctor if you are taking any of the following medicines used to treat high blood pressure:

• an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.

• aliskiren

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not take **OLSAR H** ".

Tell your doctor if you have any of the following health problems:

• Kidney problems

• Liver disease

• Heart failure or problems with your heart valves or heart muscle

• Severe vomiting, diarrhoea, treatment with high doses of water tablets (diuretics) or if you are on a low salt diet

• Increased levels of potassium in your blood

• Problems with your adrenal glands.

Contact your doctor if you experience diarrhoea that is severe, persistent and causes substantial weight loss. Your doctor may evaluate your symptoms and decide on how to continue your blood pressure medication.

As with any medicine which reduces blood pressure, an excessive drop in blood pressure in patients with blood flow disturbances of the heart or brain could lead to a heart attack or stroke. Your doctor will therefore check your blood pressure carefully.

You must tell your doctor if you think you are (or might become) pregnant. Olmesartan Tablets are not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Other medicines and OLSAR -H Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor or pharmacist about any of the following:

• Other blood pressure lowering medicines, as the effect of OLSAR -H Tablets can be increased. Your doctor may need to change your dose and/or to take other precautions:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take OLSAR -H Tablets" and "Warnings and precautions").

• Potassium supplements, a salt substitute which contains potassium, water tablets (diuretics) or heparin (for thinning the blood). Using these medicines at the same time as OLSAR -H Tablets may raise the levels of potassium in your blood.

• Lithium (a medicine used to treat mood swings and some types of depression) used at the same time as OLSAR -H Tablets may increase the toxicity of lithium. If you have to take lithium, your doctor will measure your lithium blood levels.

• Non-Steroidal Anti-Inflammatory (NSAIDs) medicines (medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis) used at the same time as OLSAR -H Tablets may increase the risk of kidney failure and the effect of OLSAR -H Tablets can be decreased by NSAIDs.

• Colesevelam hydrochloride, a drug that lowers the level of cholesterol in your blood, as the effect of OLSAR -H may be decreased. Your doctor may advise you to take OLSAR -H at least 4 hours before colesevelam hydrochloride.

• Certain antacids (indigestion remedies), as the effect of OLSAR -H Tablets can be slightly decreased.

Older people

If you are over 65 years of age and your doctor decides to increase your dose of OLSAR -H medoxomil to 40mg daily, then you need to have your blood pressure regularly checked by your doctor to make sure that your blood pressure does not become too low.

Black patients

As with other similar drugs the blood pressure lowering effect of OLSAR -H Tablets is somewhat less in black patients.

OLSAR -H Tablets with food and drink

OLSAR -H Tablets can be taken with or without food.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking OLSAR -H Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of OLSAR -H Tablets. OLSAR -H Tablets are not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. OLSAR -H Tablets are not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

You may feel sleepy or dizzy while being treated for your high blood pressure. If this happens, do not drive or use machines until the symptoms wear off. Ask your doctor for advice.

9.3 How to take OLSAR -H Tablets

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

In patients with mild to moderate kidney disease, your dose will not be higher than 20mg once a day.

The tablets can be taken with or without food. Swallow the tablets with a sufficient amount of water (e.g. one glass). If possible, take your daily dose at the same time each day, for example at breakfast time. The tablet should be swallowed whole and not chewed.

If you take more OLSAR -H Tablets than you should

If you take more tablets than you should or if a child accidentally swallows some, go to your doctor or nearest emergency department immediately and take your medicine pack with you.

If you forget to take OLSAR -H Tablets

If you forget a dose, take your normal dose on the following day as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking OLSAR -H Tablets

It is important to continue to take OLSAR -H Tablets unless your doctor tells you to stop. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If they do occur, they are often mild and do not require treatment to be stopped.

Although not many people may get them, the following two side effects can be serious:

On rare occasions (may affect up to 1 in 1,000 people) the following allergic reactions that may affect the whole body have been reported:

Swelling of the face, mouth and/or larynx (voice box) together with itching and rash may occur during treatment with OLSAR -H Tablets. **If this happens stop taking OLSAR -H Tablets and contact your doctor immediately.**

Rarely (but slightly more often in older people) OLSAR -H Tablets can cause the blood pressure to fall too low in susceptible individuals or as the result of an allergic reaction. This could cause severe light-headedness or fainting. If this occurs stop taking OLSAR -H Tablets, contact your doctor immediately and lie down flat.

These are the other side effects known about so far with OLSAR -H Tablets:

Common side effects (may affect up to 1 in 10 people):

Dizziness, headache, nausea, indigestion, diarrhoea, stomach ache, gastroenteritis, tiredness, sore throat, runny or stuffy nose, bronchitis, flu-like symptoms, cough, pain, pain in the chest, back, bones or joints, infection of the urinary tract, swelling of ankles, feet, legs, hands or arms, blood in the urine.

Some changes in blood test results have also been seen and include the following:

Increased fat levels (hypertriglyceridaemia), increased uric acid levels (hyperuricaemia), rise in blood urea, increases in tests of liver and muscle function.

Uncommon side effects (may affect up to 1 in 100 people):

Quick allergic reactions that may affect the whole body and may cause breathing problems as well as a rapid fall of blood pressure that may even lead to fainting (anaphylactic reactions), swelling of the face, vertigo, vomiting, weakness, feeling unwell, muscular pain, skin rash, allergic skin rash, itching, exanthema (skin eruption), skin lumps (wheals), angina (pain or uncomfortable feeling in the chest). In blood tests a reduction of the numbers of a type of blood cell, known as platelets has been seen (thrombocytopenia).

Rare side effects (may affect up to 1 in 1,000 people):

Lack of energy, muscle cramps, impaired kidney function, kidney failure.

Some changes in blood test results have also been seen. These include increased potassium levels (hyperkalaemia) and increased levels of compounds related to kidney function.

Additional side effects in children and adolescents:

In children, side effects are similar to those reported in adults. However, dizziness and headache are seen more often in children, and nose bleeding is a common side effect seen in children only.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store OLSAR -H Tablets

Store in a cool and dry place. Protect from light & moisture. Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

What OLSAR -H Tablets contain

• **The active substance is:** Olmesartan Medoxomil I.P 20mg/40mg and Hydrochlorothiazide I.P.12.5mg

OLSAR - H 20

Olmesartan Medoxomil I.P. 20mg and Hydrochlorothiazide I.P. 12.5mg

The excipients used are Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Yellow.

OLSAR – H 40

The excipients used are Microcrystalline Cellulose, Lactose, Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc and Ferric Oxide Red.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135

11. Details of permission or licence number with date.

Mfg Licence No.: M/563/2010 issued on 20.11.2017

12. Date of revision

Not Applicable

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/ OLSAR - H 20,12.5,40, 12.5 mg/Aug-20 /01/PI