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

OLSAR CH

1. Generic Name

Chlorthalidone and Olmesartan Medoxomil Tablets

2. Qualitative and quantitative composition

OLSAR CH 20/6.25

Each film-coated tablet contains:

Chlorthalidone I.P. ……..……6.25 mg

Olmesartan Medoxomil I.P. ……...20 mg

Excipients……. q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000 And Castor Oil.

OLSAR CH 20/12.5

Each film coated tablet contains:

Chlorthalidone I.P. ……..……12.5 mg

Olmesartan Medoxomil I.P. ……...20 mg

Excipients……. q.s.

Colour: Ferric Oxide Yellow NF

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

OLSAR CH 40/12.5

Each film coated tablet contains:

Chlorthalidone I.P. ……..……12.5 mg

Olmesartan Medoxomil I.P. ……....40 mg

Excipients……. q.s.

Colour: Ferric Oxide Yellow NF

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

3. Dosage form and strength

Dosage Form: Film Coated Tablet

Strengths: Chlorthalidone 6.25/12.5/12.5 mg and Olmesartan Medoxomil 20/20/40 mg Tablets

4. Clinical particulars

4.1 Therapeutic Indication

Treatment of essential hypertension.

4.2 Posology and Method of Administration

Dosage: As directed by the Physician

4.3 Contraindications

- Known hypersensitivity to chlortalidone or any of the excipients. Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), hypersensitivity to chlortalidone and other sulphonamide derivatives, refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia (history of gout or uric acid calculi), hypertension during pregnancy, untreated Addison's disease and concomitant lithium therapy.
- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimesters of pregnancy.
- Biliary obstruction.
- The concomitant use of Olmesartan medoxomil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4 Special Warnings and Precautions for Use

Chlorthalidone

Warnings:

Chlortalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis.

Chlortalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

Precautions:

Electrolytes:

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hyperglycaemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by Chlortalidone is dose dependent and varies in extent from one subject to another. With 25 to 50mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l. Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients.

If necessary, Chlortalidone may be combined with oral potassium supplements or a potassium-sparing diuretic (eg triamterene).

If hypokalaemia is accompanied by clinical signs (eg muscular weakness, paresis and ECG alteration), Chlortalidone should be discontinued.

Combined treatment consisting of Chlortalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (eg nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, Chlortalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlortalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlortalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlortalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

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, 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). 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 (ie 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.

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 older people, 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), 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.

Lithium:

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

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 gastroenterologist) 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 antagonists 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.

Paediatric population:

Olmesartan is not recommended in children below 1 year of age as no experience is available.

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.

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.

4.5 Drugs Interactions

Chlorthalidone

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias.

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of Chlortalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (eg atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

Olmesartan Medoxomil

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.

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. Such concomitant use is therefore not recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses > 3g/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. 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.

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.

Chlorthalidone

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.

Chlortalidone passes into the breast milk; mothers taking Chlortalidone should refrain from breast-feeding their infants.

Olmesartan Medoxomil

Pregnancy

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II antagonists is contra-indicated during the 2nd and 3rd 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). (See also 5.3 “Preclinical Safety Data”.)

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.

Breast-feeding

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 during breast-feeding, Olmesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on Ability to Drive and Use Machines

Chlorthalidone

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

Olmesartan Medoxomil

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

4.8 Undesirable Effects

Chlorthalidone

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%; uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.

Uncommon: gout.

Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.

Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria and other forms of skin rash.

Rare: photosensitisation.

Liver:

Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:

Common: postural hypotension.

Rare: cardiac arrhythmias.

Central nervous system:

Common: Dizziness.

Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite and minor gastrointestinal distress.

Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.

Very rare: pancreatitis.

Blood:

Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects:

Common: impotence

Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

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).

MedDRA 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	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

Elderly (age 65 years or over):

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

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.

4.9 Overdose

Chlorthalidone

Signs and symptoms: In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment: There is no specific antidote to Chlortalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

Olmesartan Medoxomil

Only limited information is available regarding over dosage in humans. The most likely effect of overdosage is hypotension. In the event of over dosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of olmesartan.

5. Pharmacological properties

5.1 Mechanism of Action

Chlorthalidone

Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the $Na+Cl^-$ cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

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.

5.2 Pharmacodynamic Properties

Chlorthalidone

Chlortalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action. In persons with normal renal function, diuresis is induced after the administration of 12.5mg Chlortalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, chlortalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Chlortalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Chlortalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlortalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensives potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

In renal diabetes insipidus, Chlortalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

Olmesartan Medoxomil

Pharmacotherapeutic group: Angiotensin II antagonists, ATC code: C09C A 08.
Clinical efficacy and safety

In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of 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. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment. When used together with

hydrochlorothiazide, the reduction in blood pressure is additive and coadministration is well tolerated.

The effect of olmesartan on mortality and morbidity is not yet known.

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3.2 years, patients received either olmesartan or placebo in addition to other antihypertensive agents, except ACE inhibitors or ARBs.

For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2% (178 of 2160) of the patients in the olmesartan group and 9.8% (210 of 2139) in the placebo group developed microalbuminuria.

For the secondary endpoints, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients (0.7%) vs. 3 patients (0.1%)), despite similar rates for non-fatal stroke (14 patients (0.6%) vs. 8 patients (0.4%)), non-fatal myocardial infarction (17 patients (0.8%) vs. 26 patients (1.2%)) and non-cardiovascular mortality (11 patients (0.5%) vs. 12 patients (0.5%)). Overall mortality with olmesartan was numerically increased (26 patients (1.2%) vs. 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events.

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) investigated the effects of olmesartan on renal and cardiovascular outcomes in 577 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3.1 years, patients received either olmesartan or placebo in addition to other antihypertensive agents including ACE inhibitors.

The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all-cause death) occurred in 116 patients in the olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (HR 0.97 (95% CI 0.75 to 1.24); p=0.791). The composite secondary cardiovascular endpoint occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5%) patients receiving olmesartan versus 3 (1.1%) receiving placebo, overall mortality 19 (6.7%) versus 20 (7.0%), non-fatal stroke 8 (2.8%) versus 11 (3.9%) and non-fatal myocardial infarction 3 (1.1%) versus 7 (2.5%), respectively.

Other information:

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or

hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population:

The antihypertensive effects of olmesartan in the paediatric population were evaluated in a randomized, double-blind, placebo-controlled study in 302 hypertensive patients aged 6 to 17 years. The study population consisted of an all-black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 blacks. The aetiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 mg (low dose) or 20 mg (high dose) of olmesartan once daily and patients who weighed ≥35 kg were randomized to 5 mg (low dose) or 40 mg (high dose) of olmesartan once daily. Olmesartan significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmesartan at both low and high doses significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from the baseline, respectively. This effect was also observed during the 2 weeks randomized withdrawal phase, whereby both mean systolic and diastolic blood pressures demonstrated a statistically significant rebound in the placebo group compared to olmetec group. The treatment was effective in both, paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥5 kg received 0.3 mg/kg of olmesartan once daily for three weeks in an open label phase and then were randomized to receiving olmesartan or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was 3/3 mmHg lower in the group randomized to olmesartan; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/-1 to 7).

5.3 Pharmacokinetic Properties

Chlorthalidone

Absorption and plasma concentration

The bioavailability of an oral dose of 50mg Chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, Cmax values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24-hour dosage interval, are reached after 1 to 2 weeks.

Distribution

In blood, only a small fraction of chlortalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlortalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlortalidone is about 76% and the major binding protein is albumin.

Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.

Elimination

Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special patient groups

Renal dysfunction does not alter the pharmacokinetics of chlortalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

No dosage adjustment is needed in patients with impaired renal function.

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlortalidone.

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.

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

Older people (age 65 years or older):

In hypertensive patients, the AUC at steady state was increased by ca 35% in older people (65 – 75 years old) and by ca 44% in very old people (≥ 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.

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.

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.

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 Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.

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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Chlorthalidone

There are no pre-clinical data of relevance to the prescribe

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.

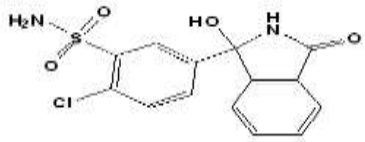
Olmesartan medoxomil was not carcinogenic, neither in rats in a 2-year study nor in mice when tested in two 6-month carcinogenicity studies using transgenic models.

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 fetotoxic effect.

7. DESCRIPTION

Chlorthalidone

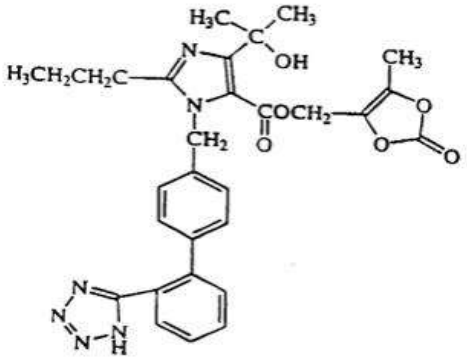
Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



Chlorthalidone is a white to yellowish-white, crystalline powder which is soluble in methanol; slightly soluble in ethanol (95%); practically insoluble in water, in ether and in chloroform.

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.

OLSAR CH 20/6.25

Chlorthalidone and Olmesartan Medoxomil Tablets are white, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000 And Castor Oil.

OLSAR CH 20/12.5

Chlorthalidone and Olmesartan Medoxomil Tablets are yellow coloured, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

OLSAR CH 40/12.5
Chlorthalidone and Olmesartan Medoxomil Tablets are yellow coloured, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

8. Pharmaceutical particulars

8.1 Incompatibilities
None Stated

8.2 Shelf-life
Do not use later than date of expiry.

8.3 Packaging information
OLSAR CH is available in strip of 10 tablets.

8.4 Storage and Handing Instructions
Store in a cool and dry place. Protect from light and moisture.
Keep all medicines out of reach of children.

9. PATIENT COUNSELLING INFORMATION

OLSAR CH

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

The information in this leaflet has been divided into the following sections:

9.1 What OLSAR CH is and what it is taken for

OLSAR CH is combination of two molecules Olmesartan and Chlorthalidone. Olmesartan belongs to a group of medicines called thiazide diuretics. Chlorthalidone belongs to a group of medicines called thiazide diuretics. Thiazide diuretics help to reduce the amount of water in your body. They do this by increasing the amount of water that you pass as urine. They are sometimes called 'water tablets'.

Thiazide diuretics help to reduce the amount of water in your body. They do this by increasing the amount of water that you pass as urine. They are sometimes called 'water tablets'.

Olsar CH is used for the treatment of high blood pressure (also known as 'hypertension'). High blood pressure can damage blood vessels in organs such as the heart, kidneys, brain and eyes. In some cases, this may lead to a heart attack, heart or kidney failure, stroke or blindness. Usually high blood pressure has no symptoms. It is important to have your blood pressure checked to prevent damage occurring.

High blood pressure can be controlled with medicines such as Olsar CH. Your doctor has probably also recommended that you make some changes in your lifestyle to help lower your blood pressure (for example losing weight, giving up smoking, reducing the amount of alcohol you drink and reducing the amount of salt in your diet). Your doctor may also have urged you to take regular exercise, such as walking or swimming. It is important to follow this advice from your doctor.

9.2 What you need to know before you take OLSAR CH

Do not take **OLSAR CH**

Tablets:

• if you are allergic to **OLSAR CH** 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.

you are not passing any urine at all

• if you have severe kidney or liver problems

• if you have low blood levels of potassium which can cause muscle weakness,

muscle twitching or abnormal heartbeat

if you have high blood levels of calcium which can cause loss of appetite,

tiredness or muscle weakness

• if you have ever had gout or kidney stones

• if you have Addison's disease (which is a condition where your adrenal gland

is not producing enough steroids)

- If you have severe low blood pressure (hypotension).

- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.

Warnings and precautions

Talk to your doctor before taking OLSAR CH.

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 CH".

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.

• Liver disease

• You are elderly and your dose needs to be increased

• you suffer from any other liver or kidney problems

• you are on a low-salt diet

• you suffer from diabetes mellitus (increased levels of sugar in the blood)

• you have high cholesterol levels

• if you have recently had an anaesthetic

• you are elderly.

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 CH** 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 CH 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 CH 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 CH 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 CH 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 CH Tablets may increase the risk of kidney failure and the effect of OLSAR CH Tablets can be decreased by NSAIDs.

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

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

- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St. John’s Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities)
- tacrolimus, sirolimus, temsirolimus, and everolimus (medicines used to alter the way your
- immune system works)
- simvastatin (cholesterol lowering medicine)
- cyclosporine (an immunosuppressant)

- beta blockers (for example propranolol hydrochloride) - methyldopa - vasodilators (for example bosentan) guanethidine

• adrenocorticotropic hormone (ACTH) - used to treat a number of different conditions, including ulcerative colitis, Crohn's disease and rheumatoid arthritis

• corticosteroids such as prednisolone or betamethasone - used to treat allergic and inflammatory diseases and immune reactions

• anticholinergics such as atropine sulphate or hyoscine butyl bromide - for abdominal or stomach spasms or cramps

• cytotoxic agents such as cyclophosphamide or methotrexate - used to treat cancer

• colestyramine - used to reduce cholesterol levels and prevent heart disease

• asthma treatments such as salbutamol or formoterol

• amantadine - used to treat Parkinson's disease or viral infections

• amphotericin - used to treat infections

• allopurinol - used to treat gout

• carbenoxolone - used to treat ulcers • calcium salts or vitamin D - used for replacement therapy

• insulin and other treatments for diabetes such as chlorpropamide or glibenclamide - used for pain relief or rheumatism

• digoxin - for an irregular heartbeat

• ciclosporin - used to treat rheumatic disease or skin complaints or after a transplant

Older people

If you are over 65 years of age and your doctor decides to increase your dose of OLSAR CH 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 CH Tablets is somewhat less in black patients.

OLSAR CH Tablets with food and drink

OLSAR CH Tablets can be taken with or without food.

Grapefruit juice and grapefruit should not be consumed by people who are taking OLSAR CH. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient OLSAR CH, which can cause an unpredictable increase in the blood pressure lowering effect of OLSAR CH.

Pregnancy and breast-feeding

Pregnancy and breast-feeding Do not take OLSAR CH if you are pregnant or trying to become pregnant. Do not take OLSAR CH if you are breast-feeding because OLSAR CH passes into breast milk and could harm your baby. Ask your doctor or pharmacist for advice before taking any medicine. Ask your doctor or pharmacist for advice before taking any 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 CH Tablets

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

Dosage: As directed by the Physician.

If you take more **OLSAR CH** 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 CH 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 CH Tablets

It is important to continue to take OLSAR CH 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 CH Tablets. **If this happens stop taking OLSAR CH Tablets and contact your doctor immediately.**

Rarely (but slightly more often in older people) OLSAR CH 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 CH Tablets, contact your doctor immediately and lie down flat.

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

Very common side effects (that affect more than 1 person in 10)

• low blood levels of potassium which can cause muscle weakness, muscle twitching or abnormal heartbeat • increased blood levels of uric acid

• increased blood levels of cholesterol.

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. low levels of sodium which can cause tiredness, confusion, muscle twitching, fits or coma \

• low levels of magnesium

• high blood sugar levels which can cause tiredness, weakness or feeling thirsty

• nettle rash

• skin rash

• low blood pressure which may make you feel dizzy when you stand up

• dizziness

• loss of appetite

• upset stomach

• impotence in men.

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).Mood changes, anxiety, depression, sleeplessness, Cough, Dry mouth, vomiting (being sick).Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration

- Disorder in passing urine, increased need to urinate at night, increased number of times of
- passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Pain, feeling unwell
- Joint or muscle pain, back pain
- Weight increase or decrease

gout which causes pain and swelling in the joints.

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.

Confusion.

• increased calcium in the blood which can cause agitation, sore eyes,

abdominal pain

• sugar in the urine (this would show up when your doctor or nurse tests your

urine)

• worsening of diabetes

• yellowing of the skin or eyes caused by liver or blood problems (jaundice)

• increased sensitivity of your skin to sunlight

• abnormal heartbeat the symptoms of which include palpitations and fainting

• pins and needles

• headache

• feeling or being sick

• stomach pain

• constipation

• diarrhoea

• reduction in blood platelets which increases the risk of bruising or bleeding

• severe reduction in the number of white blood cells which makes infection more likely

• an abnormally high amount of eosinophils (type of white blood cell) in the blood

• breathing problems

• problems with your kidneys.

Very rare: may affect up to 1 in 10,000 people

- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause muscular weakness, tingling or numbness
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin
- (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

• low levels of chloride in the blood, symptoms include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension

• inflammation of the pancreas which causes severe stomach and back pain.

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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store OLSAR CH

Store in a cool and dry place. Protect from light and moisture.

Keep all medicines out of reach of children.

9.6. Contents of the pack and other information

OLSAR CH is available in strip of 10 tablets.

OLSAR CH 20/6.25

Each film-coated tablet contains:

Chlorthalidone 6.25 mg and Olmesartan Medoxomil 20 mg

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000 And Castor Oil.

OLSAR CH 20/12.5

Each film coated tablet contains:

Chlorthalidone 12.5 mg and Olmesartan Medoxomil 20 mg

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

OLSAR CH 40/12.5

Each film coated tablet contains:

Chlorthalidone 12.5 mg and Olmesartan Medoxomil I.P 40 mg

The excipients used are Lactose, Microcrystalline Cellulose Powder, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Starch, Magnesium Stearate, Aerosil, Croscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Ethyl Cellulose, Talc, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow NF.

10. Details Of Manufacturer

Manufactured in India by:

GKM New Pharma

Spl Type Plot No.: 5, 6, 7 & 8, PIPDIC, Electronic Park,

Thirubuvanai, Puducherry-605107.

11. Details Of Permission Or Licence Number With Date

Mfg Lic No. 09 13 2634 issued on 01.12.2016.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ OLSAR CH 6.25 +20, 12.5 + 20 and 12.5 + 40 mg/Feb-21/01/PI