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

OLSAR -A

1. Generic Name

Amlodipine and Olmesartan Medoxomil Tablets U.S.P.

2. Qualitative and quantitative composition

OLSAR-A 20

Each Film Coated tablet contains:

Amlodipine Besylate I.P.

equivalent to Amlodipine…….5mg

Olmesartan Medoxomil I.P…….20mg

Colours: Indigo Carmine Aluminium Lake and Titanium Dioxide I.P.

Excipients…….q.s.

The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry II 85F80903 Blue.

OLSAR-A 40

Each Film Coated tablet contains:

Amlodipine Besylate I.P.

equivalent to Amlodipine…….5mg

Olmesartan Medoxomil I.P…….40mg

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

Excipients…….q.s.

The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Instacoat Universal A05D00904 (Yellow).

3. Dosage form and strength

Dosage: Film coated tablet

Strength: Olmesartan Medoxomil I. P 20mg/40mg and Amlodipine 5mg

4. Clinical particulars

4.1 Therapeutic Indication

OLSAR-A 20

For the treatment of mild to moderate hypertension.

OLSAR-A 40

Additional indication:

1. for the treatment of hypertension alone or with other antihypertensive agents

2. To use as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

4.2 Posology and Method of Administration

Posology

Dosage: As directed by the Physician.

Method of administration

Tablet for oral administration.

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 containing Tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction. 4.4 Special warnings and precautions for use

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). 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.

Amlodipine

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when

increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

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.

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.

Amlodipine

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous Dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin

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

Olmesartan Medoxomil

Pregnancy

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.

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.

Amlodipine

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility

4.7 Effects on ability to drive and use machines

Olsar –A can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

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
	Leukocytopenia, thrombocytopenia	Very rare
Immune system disorders	Anaphylactic reaction	Uncommon
	Allergic reactions	Very rare

Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
	Hyperglycaemia	Very rare
Nervous system disorders	Somnolence, dizziness, headache (especially at the beginning of the treatment)	Common
	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia	Uncommon
	Hypertonia, peripheral neuropathy	Very rare
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Palpitations	Common
	Angina pectoris Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon
	Myocardial infarction	Very rare
Vascular disorders	Common	Flushing
	Very rare	Vasculitis
	Hypotension	Unknown
Respiratory, thoracic and mediastinal disorders	Bronchitis, Dyspnoea	Common
	Pharyngitis	Common
	Cough, Rhinitis	Unknown
Gastrointestinal disorders	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)	Common
	Vomiting, dry mouth	Uncommon
	Sprue-like enteropathy (see section 4.4) Pancreatitis, gastritis, gingival hyperplasia Hepatitis, jaundice, hepatic enzyme increased*	Very rare
Skin and subcutaneous tissue disorders	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, urticaria, Allergic dermatitis	Uncommon
	erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity	Very rare
	Angioedema	Rare

	Toxic epidermal necrolysis	Not known
Musculoskeletal and connective tissue disorders	Ankle swelling, muscle cramps	Common
	Arthralgia.	Uncommon
	Muscle spasm	Rare
	Back pain, Myalgia	Not known
Renal and urinary disorders	Haematuria	Common
	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
	Micturition disorder, nocturia, increased urinary frequency	Uncommon
General disorders and administration site conditions	Oedema	Very common
	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
	Weight increased, weight decreased	Uncommon

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.

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.

Amlodipine

In humans, experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

5.2Pharmacodynamicproperties

Pharmacotherapeutic group: Angiotensin II antagonists, ATC code: C09C A 08.

Mechanism of action/ Pharmacodynamic effects

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.

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 reported 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.

Paediatric population

The antihypertensive effects of olmesartan medoxomil 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 medoxomil once daily and

patients who weighed ≥35 kg were randomized to 5 mg (low dose) or 40 mg (high dose)of olmesartan medoxomil once daily. Olmesartan medoxomil significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmesartan medoxomil 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 olmesartan 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 medoxomil once daily for three weeks in an open label phase and then were randomized to receiving olmesartan medoxomil 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 medoxomil; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/ -1 to 7).

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.

Amlodipine

Table 1. Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002

Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24
Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.					

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine had no effect on total cardiovascular mortality. In this same population Amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Use in children (aged 6 years and older)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

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.

Pharmacokinetic/ s 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

Amlodipine

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly population

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

6. Nonclinical properties

6.1 Animal Toxicology

Olmesartan Medoxomil

In reported 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.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

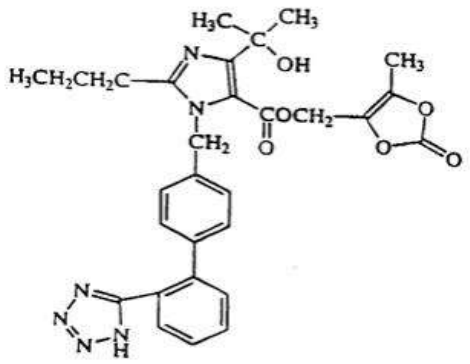
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

7. Description

Olmesartan Medoxomil

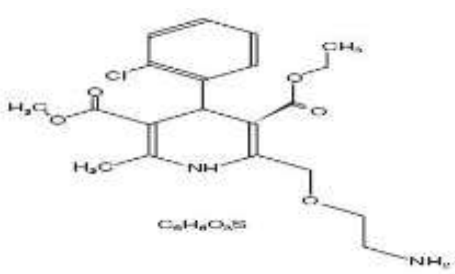
Olmesartan Medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan medoxomil is chemically described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. 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.

Amlodipine Besylate

Amlodipine Besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene-sulphonate. Its molecular formula is $C_{20}H_{25}CIN_2O_5 \bullet C_6H_6O_3S$, and its structural formula is:



Amlodipine Besylate is a white or almost white powder with a molecular weight of 567.1. it is freely soluble in methanol; sparingly soluble in ethanol (95 percent); slightly soluble in 2-propanol and in water.

OLSAR-A 20

Amlodipine and Olmesartan Tablets light to dark blue coloured, round, biconvex, film coated tablets plain on both sides. The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry II 85F80903 Blue.

OLSAR-A 40

Amlodipine and Olmesartan Tablets light yellow to yellow coloured, round, biconvex, film coated tablets with break line on one side and plain on other side. The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Instacoat Universal A05D00904 (Yellow).

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-A is available in blister strip of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, Protected from moisture.

Keep out of reach of children.

9. Patient Counselling Information

OLSAR - A

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 -A is and what it is used for

OLSAR -A is combination of the active substance Olmesartan Tablets and Amlodipine belongs to a group of medicines called calcium antagonists. In patients with high blood pressure Amlodipine works by relaxing blood vessels, so that blood passes through.

Your doctor has probably also recommended that you make some changes to 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.

OLSAR-A 20

For the treatment of mild to moderate hypertension.

OLSAR-A 40

Additional indication: 1. for the treatment of hypertension alone or with other antihypertensive agents 2. To use as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

9.2 What you need to know before you take OLSAR -A

Do not take OLSAR -A

Tablets:

• If you are allergic to **OLSAR -A** 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.

- 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 -A**.

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.

You should inform your doctor if you have or have had any of the following conditions:

- Recent heart attack
- Heart failure or problems with your heart valves or heart muscle
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- Kidney problems
- Severe vomiting, diarrhoea, treatment with high doses of water tablets (diuretics) or if you are on a low salt diet
- You are elderly and your dose needs to be increased
- 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 -A 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 -A 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 -A 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 -A 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 -A 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 -A Tablets may increase the risk of kidney failure and the effect of OLSAR -A Tablets can be decreased by NSAIDs.

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

• Certain antacids (indigestion remedies), as the effect of OLSAR -A 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)

Older people

If you are over 65 years of age and your doctor decides to increase your dose of OLSAR -A 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.

OLSAR -A with food and drink

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

Pregnancy and breast-feeding

Pregnancy

The safety of OLSAR -A in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take OLSAR -A.

Breast-feeding

OLSAR -A has been shown to pass into breast milk in small amounts. If you are breast-feeding or about to start breast-feeding, you must tell your doctor before taking OLSAR -A.

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 -A 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 -A 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 -A 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 -A Tablets

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

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

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

Visit your doctor **immediately** if you experience any of the following side effects after taking this medicine.

- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell
- The following very common side effect has been reported. If this causes you problems or if it lasts for more than one week, you should contact your doctor.
  Very common: may affect more than 1 in 10 people
- Oedema (fluid retention)

The following **common side effects** have been reported. If any of these cause you problems or if they **last for more than one week**, you should **contact your doctor.**

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.
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Altered bowel habits, diarrhoea, constipation, indigestion
- Tiredness, weakness
- Visual disturbances, double vision
- Muscle cramps
- Ankle swelling

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).
- 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

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.

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

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 -A Tablets

Store at a temperature not exceeding 30°C, Protected from moisture.

Keep out of reach of children.

9.6 Contents of the pack and other information

What OLSAR -A Tablets contain

• The active substance is

Olmesartan Medoxomil 20mg & Amlodipine Besilate 5mg Tablets and
Olmesartan Medoxomil 40mg & Amlodipine Besilate 5mg Tablets

• The other ingredients are:

OLSAR-A 20

The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry II 85F80903 Blue.

OLSAR-A 40

The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Starlac, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Instacoat Universal A05D00904 (Yellow).

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceutical Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim – 737135.

11. Details of permission or licence number with date.

Mfg Lic No. M/563/2010 issued on 12.03.2020

12. Date of revision

Not Applicable

MARKETED BY

IN/ OLSAR -A 20,5,40, 5 mg/Aug-20/01/PI