

OLMETOR AM

1. Generic Name

Olmesartan Medoxomil and Amlodipine Besilate Tablets

2. Qualitative and quantitative composition

OLMETOR AM 20

Each film coated tablet contains:

Olmesartan Medoxomil I.P. 20 mg

Amlodipine Besilate I.P.

Equivalent to Amlodipine 5 mg

Colour: Titanium Dioxide I.P.

The excipients used are Lactose, MCC, Pregelatinized Starch, Croscarmellose, Sodium, colloidal silicon dioxide, magnesium stearate, Opadry II White.

OLMETOR AM 40

Each film coated tablet contains:

Olmesartan Medoxomil I.P.....40 mg

Amlodipine Besilate I.P

Equivalent to Amlodipine.....5 mg

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

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

3. Dosage form and strength

Dosage Form: Film Coated Tablets

Strength:

OLMETOR AM 20

Olmesartan Medoxomil 20 mg and Amlodipine Besilate 5 mg

OLMETOR AM 40

Olmesartan Medoxomil 40 mg and Amlodipine Besilate 5 mg

4. Clinical particulars

4.1 Therapeutic indication

OLMETOR AM 20

For the treatment of mild to moderate hypertension.

OLMETOR AM 40

For the treatment of hypertension alone or with other antihypertensive agents and 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

Adults

Olmator AM 20 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil or 5 mg amlodipine alone.

Olmator AM 40 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by Olmator AM 20 mg/5 mg.

A step-wise titration of the dosage of the individual components is recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to Olmator AM tablets containing the same component doses.

Olmator AM can be taken with or without food.

Elderly (age 65 years or over)

No adjustment of the recommended dose is generally required for elderly people but increase of the dosage should take place with care.

If up-titration to the maximum dose of 40 mg olmesartan medoxomil daily is required, blood pressure should be closely monitored.

Renal impairment

The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 20 – 60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of Olmator AM in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended.

Monitoring of potassium levels and creatinine is advised in patients with moderate renal impairment.

Hepatic impairment

Olmator AM should be used with caution in patients with mild to moderate hepatic impairment.

In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment.

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Olmator AM should therefore be administered with caution in these patients. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with impaired liver function. Use of Olmator AM in patients with severe hepatic impairment is contraindicated.

Paediatric population

The safety and efficacy of Olmetor AM in children and adolescents below 18 years has not been established. No data are available.

Method of administration:

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time each day.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipients.
- Second and third trimesters of pregnancy.
- Severe hepatic insufficiency and biliary obstruction.
- The concomitant use of Olmetor AM with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²).
- Due to the component amlodipine, Olmetor AM is also contraindicated in patients with:
 - 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

Patients with hypovolaemia or sodium depletion:

Symptomatic hypotension may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting, especially after the first dose. Correction of this condition prior to administration of Olmetor AM or close medical supervision at the start of the treatment is recommended.

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 medicinal products that affect this system, such as angiotensin II receptor antagonists, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

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

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.

Hepatic impairment:

Exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment. Care should be taken when Olmetor AM is administered in patients with mild to moderate hepatic impairment. In moderately impaired patients, the dose of olmesartan medoxomil should not exceed 20 mg. In patients with impaired hepatic function, amlodipine should be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Use of Olmetor AM in patients with severe hepatic impairment is contraindicated.

Hyperkalaemia:

As with other angiotensin II antagonists and ACE inhibitors, hyperkalaemia may occur during treatment, especially in the presence of renal impairment and/or heart failure. Close monitoring of serum potassium levels in at-risk patients is recommended.

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Lithium:

As with other angiotensin II receptor antagonists, the concomitant use of Olmetor AM and lithium is not recommended.

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:

Due to the amlodipine component of Olmetor AM, as with all 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 medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmetor AM is not recommended in such patients.

Heart failure:

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

Patients with heart failure should be treated with caution. In a reported long-term, placebo controlled study of amlodipine in patients with severe heart failure (NYHA III and IV), the reported incidence of pulmonary oedema was higher in the amlodipine 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.

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 Olmetor AM can be 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.

Elderly

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

Pregnancy:

Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.

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.

4.5 Drugs Interactions

Potential interactions related to the Olmetor AM combination:

To be taken into account with concomitant use

Other antihypertensive agents:

The blood pressure lowering effect of Olmetor AM can be increased by concomitant use of other antihypertensive medicinal products (e.g. alpha blockers, diuretics).

Potential interactions related to the olmesartan medoxomil component of Olmetor AM:

Concomitant use not recommended

ACE-inhibitors, angiotensin II receptor blockers or aliskiren:

Reported 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.

Medicinal products affecting potassium levels:

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE inhibitors) may lead to increases in serum potassium. If medicinal products which affect potassium levels are to be prescribed in combination with Olmetor AM, monitoring of serum potassium levels is recommended.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II antagonists. Therefore concomitant use of Olmetor AM and lithium is not recommended. If concomitant use of Olmetor AM and lithium proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs:

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may increase the risk of worsening of renal function and may lead to an increase in serum potassium. Therefore monitoring of renal function at the beginning of such concomitant therapy is recommended, as well as adequate hydration of the patient.

Bile acid sequestering agent colessevelam:

Concurrent administration of the bile acid sequestering agent colessevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces t_{1/2}. Administration of olmesartan medoxomil at least 4 hours prior to colessevelam hydrochloride decreased the drug interaction effect. Administering olmesartan medoxomil at least 4 hours before the colessevelam hydrochloride dose should be considered.

Additional information

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed.

Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin. Coadministration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

Olmesartan had no clinically relevant inhibitory effects on human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4 *in vitro*, and had no or minimal inducing effects on rat cytochrome P450 activities. No clinically relevant interactions between olmesartan and medicinal products metabolised by the above cytochrome P450 enzymes are expected.

Potential interactions related to the amlodipine component of Olmetor AM:

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. The clinical translation of these PK variations may be more pronounced in the elderly. There is an increased risk of hypotension. Close observation of patients is recommended 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 hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, 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 antihypertensive agents.

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

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.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. 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.

Cyclosporine: In a reported prospective study in renal transplant patients, an average 40% increase in trough cyclosporine levels was observed when used concomitantly with amlodipine. The co-administration of Olmetor AM with cyclosporine may increase exposure to cyclosporine. Monitor trough cyclosporine levels during concomitant use and cyclosporine dose reductions should be made as necessary.

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

Pregnancy

There are no data about the use of Olmetor AM in pregnant patients. Animal reproductive toxicity studies with Olmetor AM have not been performed.

Olmesartan medoxomil (active ingredient of Olmetor AM)

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II antagonists is contraindicated during the 2nd and 3rd trimesters 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 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.

Exposure to angiotensin II antagonists therapy 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 on, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II antagonists should be closely observed for hypotension.

Amlodipine (active ingredient of Olmetor AM)

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

As a consequence, Olmetor AM is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

Breastfeeding

Olmesartan is excreted into the milk of lactating rats. However, it is not known whether olmesartan passes into human milk.

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.

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

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Reported clinical data are insufficient

regarding the potential effect of amlodipine on fertility. In one reported rat study, adverse effects were found on male fertility.

4.7 Effects on ability to drive and use machines

Olmator AM can have minor or moderate influence on the ability to drive and use machines.

Dizziness, headache, nausea or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

The most commonly reported adverse reactions during treatment with Olmator AM are peripheral oedema (11.3%), headache (5.3%) and dizziness (4.5%).

Adverse reactions from Olmator AM in reported clinical trials, post-authorisation safety studies and spontaneous reporting are summarised in the below table as well as adverse reactions from the individual components olmesartan medoxomil and amlodipine based on the known safety profile of these substances.

The following terminologies have been used in order to classify the occurrence of adverse reactions:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reactions	Frequency		
		Olmесartan/Amlodipine combination	Olmесartan	Amlodipine
Blood and lymphatic system disorders	Leukocytopenia			Very rare
	Thrombocytopenia		Uncommon	Very rare
Immune system disorders	Allergic reaction /Drug hypersensitivity	Rare		Very rare
	Anaphylactic reaction		Uncommon	
Metabolism and nutrition disorders	Hyperglycaemia			Very rare
	Hyperkalaemia	Uncommon	Rare	
	Hypertriglyceridaemia		Common	
	Hyperuricaemia		Common	

Psychiatric disorders	Confusion			Rare
	Depression			Uncommon
	Insomnia			Uncommon
	Irritability			Uncommon
	Libido decreased	Uncommon		
	Mood changes (including anxiety)			Uncommon
Nervous system disorders	Dizziness	Common	Common	Common
	Dysgeusia			Uncommon
	Headache	Common	Common	Common (especially at the beginning of treatment)
	Hypertonia			Very rare
	Hypoaesthesia	Uncommon		Uncommon
	Lethargy	Uncommon		
	Paraesthesia	Uncommon		Uncommon
	Peripheral neuropathy			Very rare
	Postural dizziness	Uncommon		
	Sleep disorder			Uncommon
	Somnolence			Common
	Syncope	Rare		Uncommon
	Tremor			Uncommon
	Extrapyramidal disorder			Not known

Eye disorders	Visual disturbance (including diplopia)			Common
Ear and labyrinth disorders	Tinnitus			Uncommon
	Vertigo	Uncommon	Uncommon	
Cardiac disorders	Angina pectoris		Uncommon	Uncommon (incl. aggravation of angina pectoris)
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)			Uncommon
	Myocardial infarction			Very rare
	Palpitations	Uncommon		Common
	Tachycardia	Uncommon		
Vascular disorders	Hypotension	Uncommon	Rare	Uncommon
	Orthostatic hypotension	Uncommon		
	Flushing	Rare		Common
	Vasculitis			Very rare
Respiratory, thoracic and mediastinal disorders	Bronchitis		Common	
	Cough	Uncommon	Common	Uncommon
	Dyspnoea	Uncommon		Common
	Pharyngitis		Common	
	Rhinitis		Common	Uncommon
	Abdominal pain		Common	Common

Gastrointestinal disorders	Altered bowel habits (including diarrhoea and constipation)			Common
	Constipation	Uncommon		
	Diarrhoea	Uncommon	Common	
	Dry mouth	Uncommon		Uncommon
	Dyspepsia	Uncommon	Common	Common
	Gastritis			Very rare
	Gastroenteritis		Common	
	Gingival hyperplasia			Very rare
	Nausea	Uncommon	Common	Common
	Pancreatitis			Very rare
	Upper abdominal pain	Uncommon		
	Vomiting	Uncommon	Uncommon	Uncommon
	Sprue-like enteropathy		Very rare	
Hepato-biliary disorders	Hepatic enzymes increased		Common	Very rare (mostly consistent with cholestasis)
	Hepatitis			Very rare
	Jaundice			Very rare
Skin and subcutaneous tissue disorders	Alopecia			Uncommon
	Angioneurotic oedema		Rare	Very rare
	Allergic dermatitis		Uncommon	
	Erythema multiforme			Very rare

	Exanthema		Uncommon	Uncommon
	Exfoliative dermatitis			Very rare
	Hyperhydrosis			Uncommon
	Photosensitivity			Very rare
	Pruritus		Uncommon	Uncommon
	Purpura			Uncommon
	Quincke oedema			Very rare
	Rash	Uncommon	Uncommon	Uncommon
	Skin discoloration			Uncommon
	Stevens-Johnson syndrome			Very rare
	Toxic Epidermal Necrolysis			Not known
	Urticaria	Rare	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Ankle swelling			Common
	Arthralgia			Uncommon
	Arthritis		Common	
	Back pain	Uncommon	Common	Uncommon
	Muscle spasm	Uncommon	Rare	Common
	Myalgia		Uncommon	Uncommon
	Pain in extremity	Uncommon		
	Skeletal pain		Common	
Renal and urinary disorders	Acute renal failure		Rare	
	Haematuria		Common	

	Increased urinary frequency			Uncommon
	Micturition disorder			Uncommon
	Nocturia			Uncommon
	Pollakiuria	Uncommon		
	Renal insufficiency		Rare	
	Urinary tract infection		Common	
Reproductive system and breast disorders	Erectile dysfunction/impotence	Uncommon		Uncommon
	Gynecomastia			Uncommon
General disorders and administration site conditions	Asthenia	Uncommon	Uncommon	Common
	Chest pain		Common	Uncommon
	Face oedema	Rare	Uncommon	
	Fatigue	Common	Common	Common
	Influenza-like symptoms		Common	
	Lethargy		Rare	
	Malaise		Uncommon	Uncommon
	Oedema	Common		Very common
	Pain		Common	Uncommon
	Peripheral oedema	Common	Common	
	Pitting oedema	Common		
Investigations	Blood creatinine increased	Uncommon	Rare	

	Blood creatine phosphokinase increased		Common	
	Blood potassium decreased	Uncommon		
	Blood urea increased		Common	
	Blood uric acid increased	Uncommon		
	Gamma glutamyl transferase increased	Uncommon		
	Weight decrease			Uncommon
	Weight increase			Uncommon

Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers. Single cases of extrapyramidal syndrome have been reported in patients treated with amlodipine.

- **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.

4.9 Overdose

Symptoms

There is no experience of overdose with Olmetor AM. The most likely effects of olmesartan medoxomil overdose are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred. Amlodipine overdose can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.

Treatment

If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.

Clinically significant hypotension due to an overdose of Olmetor AM requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the 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.

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

5. Pharmacological properties

5.1 Mechanism of Action

Olmator AM is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a calcium channel blocker, amlodipine besilate. The combination of these active ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Olmesartan medoxomil (active ingredient of Olmator AM)

The olmesartan medoxomil component of Olmator AM is a selective angiotensin II type 1 (AT1) receptor antagonist. Olmesartan medoxomil is rapidly converted to the pharmacologically active metabolite, olmesartan. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Amlodipine (active ingredient of Olmator AM)

The amlodipine component of Olmator AM is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L-type channels into the heart and smooth muscle. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure.

5.2 Pharmacodynamic properties

Clinical efficacy and safety

In a reported 8-week, double-blind, randomised, placebo-controlled factorial design study in 1940 patients (71% Caucasian and 29% non-Caucasian patients), treatment with each combination dose of Olmator AM resulted in significantly greater reductions in diastolic and systolic blood pressures than the respective monotherapy components. The mean change in systolic/diastolic blood pressure was dose-dependent: -24/-14 mmHg (20 mg/5 mg combination), -25/-16 mmHg (40 mg/5 mg combination) and -30/-19 mmHg (40 mg/10 mg combination).

Olmator AM 40 mg/5 mg reduced seated systolic/diastolic blood pressure by an additional 2.5/1.7 mmHg over Olmator AM 20 mg/5 mg. Similarly Olmator AM 40 mg/10 mg reduced seated systolic/diastolic blood pressure by an additional 4.7/3.5 mmHg over Olmator AM 40 mg/5 mg.

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) were 42.5%, 51.0% and 49.1% for Olmetor AM 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg respectively.

The majority of the antihypertensive effect of Olmetor AM was generally achieved within the first 2 weeks of therapy.

A second reported double-blind, randomised, placebo-controlled study evaluated the effectiveness of adding amlodipine to the treatment in Caucasian patients whose blood pressure was inadequately controlled by 8 weeks of monotherapy with 20 mg olmesartan medoxomil.

In patients who continued to receive only 20 mg olmesartan medoxomil, systolic/diastolic blood pressure was reduced by -10.6/ -7.8 mmHg after a further 8 weeks. The addition of 5 mg amlodipine for 8 weeks resulted in a reduction in systolic/diastolic blood pressure of -16.2/-10.6 mmHg ($p = 0.0006$).

The proportion of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) was 44.5% for the 20 mg/5 mg combination compared to 28.5% for 20 mg olmesartan medoxomil.

A further study evaluated the addition of various doses of olmesartan medoxomil in Caucasian patients whose blood pressure was not adequately controlled by 8 weeks of monotherapy with 5 mg amlodipine.

In patients who continued to receive only 5 mg amlodipine, systolic/diastolic blood pressure was reduced by -9.9/ -5.7 mmHg after a further 8 weeks. The addition of 20 mg olmesartan medoxomil resulted in a reduction in systolic/diastolic blood pressure of -15.3/-9.3 mmHg and the addition of 40 mg olmesartan medoxomil resulted in a reduction in systolic/diastolic blood pressure of -16.7/-9.5 mmHg ($p < 0.0001$).

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) was 29.9% for the group who continued to receive 5 mg amlodipine alone, 53.5% for Olmetor AM 20 mg/5 mg and 50.5% for Olmetor AM 40 mg/5 mg.

Randomised data in uncontrolled hypertensive patients, comparing the use of medium dose Olmetor AM combination therapy versus escalation to top dose monotherapy of amlodipine or olmesartan, are not available.

The three reported studies confirmed that the blood pressure lowering effect of Olmetor AM once daily was maintained throughout the 24-hour dose interval, with trough-to-peak ratios of 71% to 82% for systolic and diastolic response and with 24-hour effectiveness being confirmed by ambulatory blood pressure monitoring.

The antihypertensive effect of Olmetor AM was similar irrespective of age and gender, and was similar in patients with and without diabetes.

In two reported open-label, non-randomised extension studies, sustained efficacy using Olmetor AM 40 mg/5 mg was demonstrated at one year for 49 - 67% of patients.

Olmesartan medoxomil (active ingredient of Olmetor AM)

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 abrupt cessation of therapy.

Following once daily administration to patients with hypertension, olmesartan medoxomil produces 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.

The effect of olmesartan medoxomil 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 reported 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.

Amlodipine (active ingredient of Olmetor AM)

In hypertensive patients, amlodipine 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 abrupt cessation of therapy.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces an effective reduction in blood pressure in the supine, sitting and standing positions. Chronic use of amlodipine is not associated with significant changes in heart rate or plasma catecholamine levels. In hypertensive patients with normal renal function, therapeutic doses of amlodipine reduce renal vascular resistance and increase glomerular filtration rate and effective renal plasma flow, without changing filtration fraction or proteinuria.

In reported haemodynamic studies in patients with heart failure and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

A reported placebo-controlled study (PRAISE) designed to evaluate patients with 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 in patients with heart failure.

In a reported 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 of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Treatment to prevent heart attack trial (ALLHAT)

A reported randomized 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 randomized 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).

Other information:

As per reported data, 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 reported 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.

5.3 Pharmacokinetic properties

Olmator AM

As per reported data, following oral intake of Olmator AM, peak plasma concentrations of olmesartan and amlodipine are reached at 1.5 – 2 h and 6 – 8 hours, respectively. The rate and extent of absorption of the two active substances from Olmator AM are equivalent to the rate and extent of absorption following intake of the two components as separate tablets. Food does not affect the bioavailability of olmesartan and amlodipine from Olmator AM.

Olmesartan medoxomil (active ingredient of Olmator AM)

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 active substances 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 of olmesartan 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 ¹⁴C-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 is between 10 and 15 hours after multiple oral dosing. Steady state is reached after the first few doses and no further accumulation is evident after 14 days of repeated dosing. Renal clearance is approximately 0.5 – 0.7 L/h and is independent of dose.

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 (active ingredient of Olmetor AM)

Absorption and distribution:

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 absorption of amlodipine is unaffected by the concomitant intake of food.

Biotransformation and 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.

Olmesartan medoxomil and amlodipine (active ingredients of Olmetor AM)

Special populations

Paediatric population (age below 18 years):

No pharmacokinetic data in paediatric patients are available.

Elderly (age 65 years or over):

In hypertensive patients, the olmesartan AUC at steady state is increased by ca 35% in elderly people (65 – 75 years old) and by ca 44% in very elderly 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. The recommended dosage regimen for elderly people is, however, the same, although caution should be exercised when increasing the dosage.

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 people. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in the reported study.

Renal impairment:

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

Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Hepatic impairment:

After single oral administration, olmesartan AUC values are 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 is 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC is again about 65% higher than in matched healthy controls. Olmesartan mean C_{max} values are similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. The clearance of amlodipine is decreased and the half-life is prolonged in patients with impaired hepatic function, resulting in an increase in AUC of about 40% – 60%.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Based on the non-clinical toxicity profile of each substance, no exacerbation of toxicities for the combination is expected, because each substance has different targets, i.e. the kidneys for olmesartan medoxomil and the heart for amlodipine.

In a reported 3-month, repeat-dose toxicity study of orally administered olmesartan medoxomil/amlodipine in combination in rats the following alterations were observed: decreases in red blood cell count-related parameters and kidney changes both of which might be induced by the olmesartan medoxomil component; alterations in the intestines (luminal dilatation and diffuse mucosal thickening of the ileum and colon), the adrenals (hypertrophy of the glomerular cortical cells and vacuolation of the fascicular cortical cells), and hypertrophy of the ducts in the mammary glands which might be induced by the amlodipine component. These alterations neither augmented any of the previously reported and existing toxicity of the individual agents nor induced any new toxicity, and no toxicologically synergistic effects were observed.

Olmesartan medoxomil (active ingredient of Olmetor AM)

In reported chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine; reduction in heart weight; reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of olmesartan medoxomil have also occurred in preclinical trials on other AT1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride. 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 AT1 receptor antagonists, would appear to have no clinical relevance.

Like other AT1 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 reported 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 program suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan medoxomil was not carcinogenic, in a 2-year reported study in rats nor in two 6-month carcinogenicity studies in transgenic mice.

In reported 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.

Amlodipine (active ingredient of Olmetor AM)

Reproductive toxicology

As per reported data, 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

As per reported data, 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/m² basis). In another reported 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/m² basis) was close to the maximum tolerated dose for mice but not for rats.

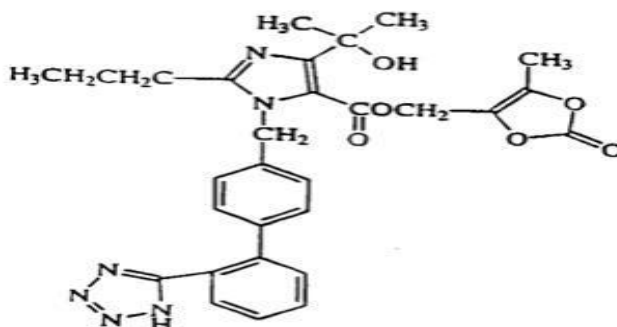
Reported mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

7. Description

Olmesartan Medoxomil

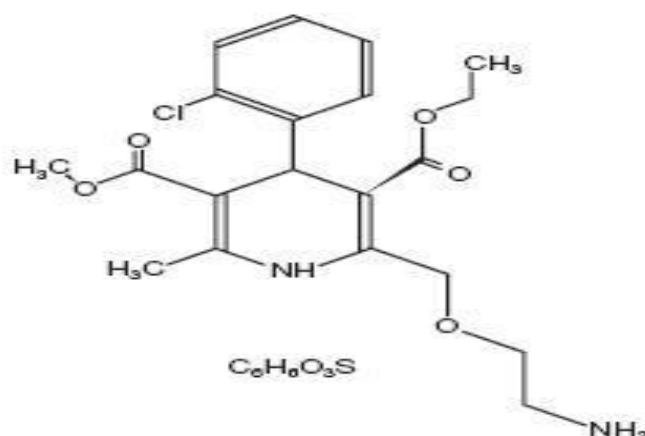
Olmesartan Medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan medoxomil is chemically described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is C₂₉H₃₀N₆O₆ 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 Besilate

Amlodipine besilate 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 C₂₀H₂₅ClN₂O₅•C₆H₆O₃S, and its structural formula is:



Amlodipine besilate 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.

OLMETOR AM 20

Olmesartan Medoxomil and Amlodipine Besilate Tablets are white to off white, round, biconvex, film coated tablets, plain on both sides. The excipients used are Lactose, MCC, Pregelatinized Starch, Croscarmellose Sodium, colloidal silicon dioxide, magnesium stearate, Opadry II White.

OLMETOR AM 40

Olmesartan Medoxomil and Amlodipine Besilate Tablets are cream to yellow colored, round, biconvex film coated tablets, plain on both sides. The excipients used are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Starlac, Talc, Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG and Yellow Oxide of Iron.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Olmetor AM 20 is packed in Blister strip of 10 tablets.

Olmetor AM 40 is packed in strip of 10 tablets.

8.4 Storage and handling instructions

Store at a temperature not exceeding 30°C, Protected from moisture. Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using 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 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. See section 9.4.

What is in this leaflet:

1. What Olmetor AM is and what it is used for
2. What you need to know before you take Olmetor AM
3. How to take Olmetor AM
4. Possible side effects
5. How to store Olmetor AM
6. Contents of the pack and other information

9.1 What Olmetor AM is and what it is used for

Olmeter AM contains two substances called olmesartan medoxomil and amlodipine (as amlodipine besilate). Both of these substances help to control high blood pressure.

- Olmesartan medoxomil belongs to a group of medicines called “angiotensin-II receptor antagonists” which lower blood pressure by relaxing the blood vessels.
- Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening thereby also reducing blood pressure.

The actions of both these substances contribute to stopping the tightening of blood vessels, so that blood vessels relax and blood pressure decreases.

Olmeter AM is used for the treatment of hypertension alone or with other antihypertensive agents and 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 use Olmetor AM

Do not use Olmetor AM if:

- you are allergic to olmesartan medoxomil or to amlodipine or a special group of calcium channel blockers, the dihydropyridines, or to any of the other ingredients of this medicine. If you think you may be allergic, talk to your doctor before taking Olmetor AM.
- you are more than 3 months pregnant (It is also better to avoid Olmetor AM in early pregnancy - see section “Pregnancy and breastfeeding”).
- you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.
- you have severe liver problems, if bile secretion is impaired or drainage of bile from the gallbladder is blocked (e.g. by gallstones), or if you are experiencing any jaundice (yellowing of the skin and eyes).

- you have very low blood pressure.
- you are suffering from insufficient blood supply to your tissues with symptoms like e.g. low blood pressure, low pulse, fast heartbeat (shock, including cardiogenic shock). Cardiogenic shock means shock due to severe heart troubles.
- the blood flow from your heart is obstructed (e.g. because of the narrowing of the aorta (aortic stenosis)).
- you suffer from low heart output (resulting in shortness of breath or peripheral swellings) after a heart attack (acute myocardial infarction).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Olmetor AM.

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 Olmetor AM”.

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

- Kidney problems or a kidney transplant.
- 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 (hormone-producing glands on top of the kidneys).

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 that you are (or might become) pregnant. Olmetor AM is 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.

Children and adolescents (under 18)

Olmeter AM is not recommended for children and adolescents under the age of 18.

Other medicines and Olmetor AM

Tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines:

- Other blood pressure lowering medicines, as the effect of Olmetor AM 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 Olmetor AM ” and “Warnings and precautions”).

- Potassium supplements, salt substitutes containing potassium, “water tablets” (diuretics) or heparin (for thinning the blood and prevention of blood clots.). Using these medicines at the same time as Olmetor AM 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 Olmetor AM may increase the toxicity of lithium. If you have to take lithium, your doctor will measure your lithium blood levels.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs, medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis) used at the same time as Olmetor AM may increase the risk of kidney failure. The effect of Olmetor AM can be decreased by NSAIDs.
- Colesevelam hydrochloride, a drug that lowers the level of cholesterol in your blood, as the effect of Olmetor AM may be decreased. Your doctor may advise you to take Olmetor AM at least 4 hours before colesevelam hydrochloride.
- Certain antacids (indigestion or heartburn remedies), as the effect of Olmetor AM can be slightly decreased.
- Medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir) or for the treatment of fungal infections (e.g. ketoconazole, itraconazole).
- Diltiazem, verapamil, (agents used for heart rhythm problems and high blood pressure).
- Rifampicin, erythromycin, clarithromycin (antibiotics), agents used for tuberculosis or other infections.
- St. John’s wort (*Hypericum perforatum*), a herbal remedy.
- Dantrolene (infusion for severe body temperature abnormalities).
- Simvastatine, an agent used to lower levels of cholesterol and fats (triglycerides) in the blood.
- Tacrolimus, cyclosporine, used to control your body’s immune response, enabling your body to accept the transplanted organ.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Olmeter AM with food and drink

Olmeter AM can be taken with or without food. Swallow the tablet with some fluid (such as one glass of water). If possible, take your daily dose at the same time each day, for example at breakfast time.

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

Elderly

If you are over 65 years of age, your doctor will regularly check your blood pressure at any dose increase, 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 Olmeter AM can be somewhat less in black patients.

Pregnancy and breast-feeding

Pregnancy

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

If you become pregnant during therapy with Olmetor AM, please inform and see your physician without delay.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Amlodipine has been shown to pass into breast milk in small amounts. Olmetor AM is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

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

Driving and using machines

You may feel sleepy, sick or dizzy or get a headache 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 use Olmetor AM

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

- The tablets can be taken with or without food. Swallow the tablet with some fluid (such as a glass of water). The tablet should not be chewed. Do not take them with grapefruit juice.
- If possible, take your daily dose at the same time each day, for example at breakfast time.

If you take more Olmetor AM than you should

If you take more tablets than you should you may experience low blood pressure with symptoms such as dizziness, fast or slow heart beat.

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 or this leaflet with you.

If you forget to take Olmetor AM

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

If you stop taking Olmetor AM

It is important to continue to take Olmetor AM 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:

Allergic reactions, that may affect the whole body, with swelling of the face, mouth and/or larynx (voice box) together with itching and rash may occur during treatment with Olmetor AM. **If this happens stop taking Olmetor AM and talk to your doctor immediately.**

Olmeter AM 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 happens stop taking Olmetor AM, talk to your doctor immediately and lie down flat.**

Other possible side effects with Olmetor AM:

Common (may affect less than 1 in 10 people):

Dizziness; headache; swelling of ankles, feet, legs, hands, or arms; tiredness.

Uncommon (may affect less than 1 in 100 people):

Dizziness on standing up; lack of energy; tingling or numbness of hands or feet; vertigo; awareness of heart beat; fast heart beat; low blood pressure with symptoms such as dizziness, light-headedness; difficult breathing; cough; nausea; vomiting; indigestion; diarrhoea; constipation; dry mouth, upper abdominal pain; skin rash; cramps; pain in arms and legs; back pain; feeling more of an urge to pass urine; sexual inactivity; inability to get or maintain an erection; weakness.

Some changes in blood test results have also been seen and include the following: increased as well as decreased blood potassium levels, increased blood creatinine levels, increased uric acid levels, increases in a test of liver function (gamma glutamyl transferase levels).

Rare (may affect less than 1 in 1,000 people):

Drug hypersensitivity; fainting; redness and warm feeling of the face; red itchy bumps (hives); swelling of face.

Side effects reported with use of olmesartan medoxomil or amlodipine alone, but not with Olmetor AM or in a higher frequency:

Olmesartan medoxomil

Common (may affect less than 1 in 10 people):

Bronchitis; sore throat; runny or stuffy nose; cough; abdominal pain; stomach flu; diarrhoea; indigestion; nausea; pain in the joints or bones; back pain; blood in the urine; infection of the urinary tract; chest pain; flu-like symptoms; pain. Changes in blood test results as increased fat levels (hypertriglyceridaemia), blood urea or uric acid increased and increase in tests of liver and muscle function.

Uncommon (may affect less than 1 in 100 people):

Reduced number of a type of blood cells, known as platelets, which can result in easily bruising or prolonged bleeding time; 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); angina (pain or uncomfortable

feeling in the chest, known as angina pectoris); itching; eruption of the skin; allergic skin rash; rash with hives; swelling of the face; muscular pain; feeling unwell.

Rare (may affect less than 1 in 1,000 people):

Swelling of the face, mouth and/or larynx (voice box); acute kidney failure and kidney insufficiency; lethargy.

Amlodipine

Very common (may affect more than 1 in 10 people):

Oedema (fluid retention)

Common (may affect less than 1 in 10 people):

Abdominal pain; nausea; ankle swelling; feeling sleepy; redness and warm feeling of the face, visual disturbance (including double vision and blurred vision), awareness of heartbeat, diarrhoea, constipation, indigestion, cramps, weakness, difficult breathing.

Uncommon (may affect less than 1 in 100 people):

Trouble sleeping; sleep disturbances; mood changes including feeling anxious; depression; irritability; shiver; taste changes; fainting; ringing in the ears (tinnitus); worsening of angina pectoris (pain or uncomfortable feeling in the chest); irregular heartbeat; runny or stuffy nose; loss of hair; purplish spots or patches on the skin due to small haemorrhages (purpura); discoloration of the skin; excessive sweating; eruption of the skin; itching; red itchy bumps (hives); pain of joints or muscles; problems to pass urine; urge to pass urine at night; increased need to urinate (pass urine); breast enlargement in men; chest pain; pain, feeling unwell; increase or decrease in weight.

Rare (may affect less than 1 in 1,000 people):

Confusion

Very rare (may affect less than 1 in 10,000 people):

Reduction in the number of white cells in the blood, which could increase the risk of infections; a reduction in the number of a type of blood cells known as platelets, which can result in easily bruising or prolonged bleeding time; increase in blood glucose; increased tightness of muscles or increased resistance to passive movement (hypertonia); tingling or numbness of hands or feet; heart attack; inflammation of blood vessels; inflammation of the liver or the pancreas; inflammation of stomach lining; thickening of gums; elevated liver enzymes; yellowing of the skin and eyes; increased sensitivity of the skin to light; allergic reactions: itching, rash, swelling of the face, mouth and/or larynx (voice box) together with itching and rash, 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), sometimes life-threatening.

Not known (frequency cannot be estimated from the available data):

Trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk.

• **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 Olmetor AM

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

9.6 Contents of the pack and other information

What Olmetor AM contains:

The active substances in this product are Olmesartan Medoxomil and Amlodipine Besilate.

OLMETOR AM 20

The excipients used are Lactose, MCC, Pregelatinized Starch, Croscarmellose Sodium, colloidal silicon dioxide, magnesium stearate, Opadry II White.

OLMETOR AM 40

The other ingredients are Silicified Microcrystalline Cellulose, Croscarmellose Sodium, Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Starlac, Talc, Polyvinyl Alcohol, Titanium Dioxide, Macrogl/PEG and Yellow Oxide of Iron..

10. Details of manufacturer

OLMETOR AM 20

TORRENT PHARMACEUTICALS LTD.

Vill, Bhud & Makhnu Majra, Teh. Baddi-173 205,

Dist. Solan (H.P.), INDIA.

OLMETOR AM 40

Manufactured by:

Pure and Cure Healthcare Pvt. Ltd.

Plot No.: 26A-30, Sector – 8A,

IIE, SIDCUL, Ranipur, Haridwar (Uttarakhand) – 249403.

11. Details of permission or licence number with date

OLMETOR AM 20

MNB/05/183 issued on 01.04.2016

OLMETOR AM 40

31/UA/2013 issued on 28.01.2016

12. Date of revision

Oct-19

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/OLMETOR AM 20+5, 40+5 /OCT-19/06/PI