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

OLSAR M

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.

1. Generic Name

Olmesartan Medoxomil & Metoprolol Succinate ER Tablets

2. Qualitative and quantitative composition

OLSAR - M 25

Each film coated bilayered tablet contains:

Olmesartan Medoxomil I.P. …….20mg
Metoprolol Succinate I.P.
Equivalent to Metoprolol Tartrate ….25mg
(As extended release)
Excipients……..….q.s.
Colours: Quinoline Yellow WS & Titanium dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Colour Quinoline Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide.

OLSAR - M 50

Each film coated bilayered tablet contains:

Olmesartan Medoxomil I.P. …….20mg
Metoprolol Succinate I.P.
Equivalent to Metoprolol Tartrate ….50mg
(As extended release)
Excipients……q.s.
Colours: Sunset Yellow FCF & Titanium dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Colour Sunset Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide.

3. Dosage form and strength

Dosage: Film coated bilayered tablet
Strength: Olmesartan Medoxomil – 20mg & Metoprolol Succinate I.P. Equivalent to Metoprolol Tartrate ….25mg/ 50mg

4. Clinical particulars

4.1 Therapeutic indication

For treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Adults

The recommended starting dose of Olsar M is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of Olsar M may be increased to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, Olsar M dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.

The antihypertensive effect of Olsar M is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose regimen for any patient.

Elderly people (65 years or older)

No adjustment of dosage is generally required in elderly people (see below for dose recommendations in patients with renal impairment). If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored.

Renal impairment

The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20-60 ml/min) is 20 mg Olsar M once daily, owing to limited experience of higher dosages in this patient group. The use of Olsar M in patients with severe renal impairment (creatinine clearance < 20 ml/min) is not recommended, since there is only limited experience in this patient group.

Hepatic impairment

No adjustment of dosage recommendations is required for patients with mild hepatic impairment. In patients with moderate hepatic impairment, an initial dose of 10 mg Olsar M 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 Olsar M in patients with severe hepatic impairment, therefore use is not recommended in this patient group. Olsar M should not be used in patients with biliary obstruction.

Paediatric population

Children and adolescents from 6 to less than 18 years of age:

The recommended starting dose of Olsar M in children from 6 to less than 18 years of age is 10 mg Olsar M once daily. In children whose blood pressure is not adequately controlled at this dose, the dose of Olsar M may be increased to 20 mg once daily. If additional blood pressure reduction is required, in children who weigh ≥ 35 kg, the Olsar M dose may be increased to a maximum of 40 mg. In children who weigh < 35 kg, the daily dose should not exceed 20 mg.

Other paediatric population

The safety and efficacy of Olsar M in children aged 1 to 5 years old have not yet been established. Currently available data are described but no recommendation on a posology can be made.

Olsar M should not be used in children below 1 year of age because of safety concerns and lack of data in this age group.

Patient should be informed that Olsar M must be swallowed whole and not chewed, cut or chrushed, and that the active ingredients may occasionally be eliminated in the feces as a soft mass that resemble the original tablet.

Method of administration

In order to assist compliance, it is recommended that Olsar M tablets be taken at about the same time each day, with or without food, for example at breakfast time. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Known hypersensitivity to metoprolol, related derivatives, and any other β-blockers or to any of the excipients.
- Second-or third-degree atrioventricular block
- Uncontrolled heart failure
- Clinically relevant sinus bradycardia (< 45-50 bpm) • Sick sinus syndrome (unless a pacemaker is in situ).
- Prinzmetal's angina
- Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock
- Severe peripheral arterial disease
- Asthma and history of bronchospasm
- Untreated phaeochromocytoma
- Metabolic acidosis
- Concomitant intravenous administration of calcium blockers of the type verapamil or diltiazem or other antiarrhythmics (such as disopyramide) is contraindicated (exception:
- intensive care unit).
- Hypotension
- Diabetes if associated with frequent episodes of hypoglycaemia
- Chronic obstructive pulmonary disease

4.4 Special warnings and precautions for use

Metoprolol Succinate

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardio selective beta blockers may have less effect on lung function than nonselective beta blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Therapy with a $beta_2$stimulant may become necessary or current therapy require adjustment. Therefore, nonselective beta blockers should not be used for these patients, and $beta_1$-selective blockers only with the utmost care.
Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta blocker should be gradual.
Metoprolol Tartrate tablets may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.
When a beta blocker is being taken, a serious, sometimes even life-threatening deterioration in cardiac function can occur, in particular in patients in whom the action of the heart is dependent on the presence of sympathetic system support. This is due less to an excessive beta-blocking effect and more to the fact that patients with marginal heart function tolerate poorly a reduction in sympathetic nervous system activity, even where this reduction is slight. This causes contractility to become weaker and the heart rate to reduce and slows down AV conduction. The consequence of this can be pulmonary oedema, AV block, and shock. Occasionally, an amlodipine Besylate g AV conduction disturbance can deteriorate, which can lead to AV block.
In patients with a phaeochromocytoma, an alpha blocker should be given concomitantly. Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.
Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, Metoprolol should be administered with caution to patients having, or suspected of developing, thyrotoxicosis, and both thyroid and cardiac function should be monitored closely.
Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to increase in blood pressure and bradycardia.
Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.
Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.
Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged release tablets than when using regular tablet forms for $beta_1$ selective beta blockers and significantly lower than when using nonselective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy.
In case of unstable or insulin dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions). In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal

insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.
Patients with anamnestic ally known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.
Beta blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.
Beta blockers may unmask myasthenia gravis.
In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose mal-absorption should not take this medicine.
Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

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.

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-angiotensinaldosterone 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.

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.

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 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.

Other

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

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

4.5 Drugs interactions

Metoprolol Succinate

- Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichloroethylene, are best avoided. In a patient under beta-blockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.
- It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculoventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.
- Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers.
- Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.
- Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-blockers used in conjunction with clonidine increase

the risk of "rebound hypertension". If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

- The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.
- NSAIDs (especially indomethacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.
- Digitalis Glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase in auriculo-ventricular conduction time.
- The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.
- The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.
- Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.
- Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolized beta blockers.
- As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.
- Class 1 antiarrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrialconduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.
- During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.
- Metoprolol may impair the elimination of lidocaine.
- Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of betablockers.
- Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen induced fluid retention may lead to increased blood pressure.
- Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects.
- Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking.
- Concurrent use requires careful monitoring.
- Concurrent use of aldesleukin may result in an enhanced hypotensive effect.
- Concurrent use of alprostadil may result in an enhanced hypotensive effect.

- There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.
- Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.
- Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.
- The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

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

4.6 Use in special populations (such as pregnancy, breast feeding, pediatric patients, geriatric patients etc.)

Metoprolol Succinate

Pregnancy

It is recommended that metoprolol should not be administered during pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant. Should therapy with metoprolol be employed, special attention should be paid to the foetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate.
Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks' gestation. Although the drug crosses the placental barrier and is present in cord blood no evidence of foetal abnormalities has been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long time treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause bradycardia in the foetus and the newborn child, there are also reports of hypoglycaemia and hypotension in newborn children.
Animal experiments have shown neither teratogenic potential nor other adverse events on the embryo and/or foetus relevant to the safety assessment of the product. Treatment with metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours post-partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Lactation

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. The risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity). Cases of neonatal hypoglycaemia and bradycardia have been described with beta-blockers with low plasma protein binding. Metoprolol is excreted in human milk. Even though the metoprolol concentration in milk is very low, breastfeeding should be discontinued during treatment with metoprolol. In case of treatment during breast feeding, infants should be monitored carefully for symptoms of beta blockade.

Olmesartan Medoxomil

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, and 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.

Breast feeding

Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Because no information is available regarding the use of Olmesartan 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.

4.7 Effects on ability to drive and use machines

As with all beta-blockers, metoprolol can affect patient's ability to drive and operate machinery. It should be taken into account that occasionally dizziness and fatigue may occur. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Metoprolol Succinate

Frequency estimates: 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); not known (cannot be estimated from the available data)

System Organ Class	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)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Thrombocytopenia, agranulocytosis	

Psychiatric disorders				Depression, nightmares, Nervousness, anxiety, impotence	Hallucinations, personality disorder, Amnesia / memory impairment	
Nervous system disorders		Dizziness, headache		Alertness decreased, somnolence or insomnia, paraesthesia		
Eye disorders					Visual disturbance (e.g. blurred vision, dry eyes and/or eye irritation	
Ear and labyrinth disorders					Tinnitus, and, in doses exceeding those recommended, "hearing disorders (eg. Hypoacusis or deafness)	
Cardiac disorders		Bradycardia		Heart failure, cardiac arrhythmias, palpitation	Cardiac conduction disorders, precordial pain	Increase in ex Amlodipi neg Besylate g intermittent claudication
Vascular disorders		Orthostatic hypotension (occasionally with syncope)		Oedema, Raynaud's phenomenon	Gangrene in patients with pre-ex Amlodipine Besylate severe peripheral circulatory disorders	

Respiratory, thoracic and mediastinal disorders		Exertional dyspnoea		Bronchospasm(which may occur in patients without a history of obstructive lung disease)	Rhinitis	
Gastrointestinal disorders		Nausea and vomiting,		Diarrhoea or constipation	Dry mouth	Retroperitoneal fibrosis *
		abdominal pain				
Hepatobiliary disorders						Hepatitis
Skin and subcutaneous tissue disorders				Skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions) s	Photosensitivity, hyperhidrosis, alopecia, worsening of psoriasis	Occurrence of antinuclear antibodies (not associated with SLE)
Musculoskeletal and connective tissue disorders				Muscle cramps	Arthritis	
Reproductive system and breast disorders					Disturbances of Libido and potency	Peyronie's disease *
General disorders and administration site conditions		Fatigue			Dysgeusia (Taste disturbances)	
Investigations					Weight increase, liver function test abnormal	

* (relationship to Metoprolol has not been definitely established).

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Olmesartan Medoxomil

Summary of the safety profile

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

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

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

Tabulated list of adverse reactions

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

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

System Organ Class	Adverse Reactions	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
Immune system disorders	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
Nervous system disorders	Dizziness	Common
	Headache	Common
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	Common
	Pharyngitis	Common
	Cough	Common
	Rhinitis	Common
Gastrointestinal disorders	Gastroenteritis	Common
	Diarrhoea	Common
	Abdominal pain	Common

	Nausea	Common
	Dyspepsia	Common
	Vomiting	Uncommon
	Sprue-like enteropathy	Very rare
Skin and subcutaneous tissue disorders	Exanthema	Uncommon
	Allergic dermatitis	Uncommon
	Urticaria	Uncommon
	Rash	Uncommon
	Pruritus	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Arthritis	Common
	Back pain	Common
	Skeletal pain	Common
	Myalgia	Uncommon
	Muscle spasm	Rare
Renal and urinary disorders	Haematuria	Common
	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
General disorders and administration site conditions	Pain	Common
	Chest pain	Common
	Peripheral oedema	Common
	Influenza-like symptoms	Common
	Fatigue	Common
	Face oedema	Uncommon
	Asthenia	Uncommon
	Malaise	Uncommon
	Lethargy	Rare
Investigations	Hepatic enzymes increased	Common
	Blood urea increased	Common
	Blood creatine phosphokinase increased	Common

	Blood creatinine increased	Rare

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

Additional information on special populations

Paediatric population:

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

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

Reportedly, 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.

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

4.9 Overdose

Metoprolol Succinate

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia. The first manifestations usually appear 20 minutes to two hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive- care ward. Absorption of any drug material still present in the gastrointestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required.

Bradycardia or extensive vagal reactions should be treated by administering atropine or methyl atropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 810mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v. infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or Haemoperfusion may be considered.

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.

5. Pharmacological properties

5.1 Mechanism of action

Metoprolol Succinate

Metoprolol Succinate is a cardio selective beta-adrenergic blocking agent. It has a relatively greater blocking effect on $beta_1$-receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on $beta_2$-receptors, which are chiefly involved in bronchi and vasodilation.

Olmesartan Medoxomil

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

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

5.2 Pharmacodynamic properties

Metoprolol Succinate

Pharmacotherapeutic category: Beta blocking agents, selective, ATC code: C07AB02
Metoprolol Succinate is a cardio selective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta -receptors (ie those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on beta -receptors, which are chiefly involved in broncho and vasodilation.

Olmesartan Medoxomil

<u>Clinical efficacy and safety</u>

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.

A reported Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 patients with type 2 diabetes, normol-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 reported 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, endstage 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 reported 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 weightadjusted 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 reported 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 reported 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 reported 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

Metoprolol Succinate

Absorption

Metoprolol is readily and completely absorbed from the gastrointestinal tract. Metoprolol is absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.

Distribution

Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ ml. Metoprolol is widely distributed, it crosses the blood brain barrier, the placenta. It is slightly bound to plasma protein. The medicinal product is approx. 5–10% bound to plasma proteins.

Biotransformation

Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as

high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute. It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the halflife of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination

The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk. *Special population* Elderly:

In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients shows no significant differences.

Renal impairment:

Renal dysfunction has barely any effect on the bioavailability of metoprolol. However, the excretion of metabolites is reduced. In patients with a glomerular filtration rate of less than 5 ml/minute, a significant accumulation of metabolites has been observed. This accumulation of metabolites, however, produces no increase in the beta blockade.

Hepatic impairment:

The pharmacokinetics of metoprolol are influenced only minimally by reduced hepatic function. However, in patients with serious hepatic cirrhosis and a portacaval shunt, the bioavailability of metoprolol can increase, and the total clearance can be reduced. Patients with portacaval anastomosis had a total clearance of approx. 0.3 litres/minute and AUC values that were 6 times higher than those found in healthy persons.

Severe angina pectoris

Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensives is influenced by this characteristic. In exceptional cases, however, very high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment

It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of preexAmlodipine Besylate g bronchospastic complaints.

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 Hepatobiliary excretion (ca 60 %). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated.

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

Pharmacokinetics in special populations

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.

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.

Drug interactions

Bile acid sequestering agent colesevelam

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam

hydrochloride. Elimination half-life of olmesartan was reduced by 50-52% irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride.

6. Nonclinical properties

6.1 Animal Toxicology

Metoprolol Succinate

There are no preclinical data of relevance to the prescriber.

Olmesartan Medoxomil

In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT_1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT_1receptors); reduction in heart weight; a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of olmesartan medoxomil have also occurred in preclinical trials on other AT_1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

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

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

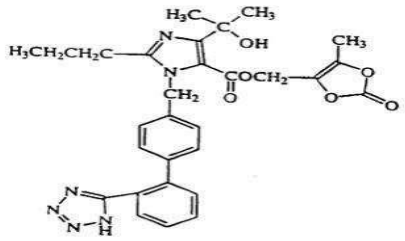
Olmesartan medoxomil was not carcinogenic, neither in rats in a 2-year reported study nor in mice when tested in two 6-month carcinogenicity studies using transgenic models.

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.

7. Description

<u>Olmesartan Medoxomil</u>

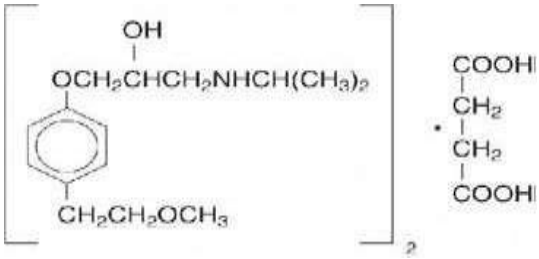
Olmesartan Medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan medoxomil is chemically described as 2, 3-dihydroxy-2butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate.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

Metoprolol Succinate

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. Its chemical name is (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt) having molecular weight of 652.81. Its empirical formula is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ with structural formula of



OLSAR M-25

Olmesartan Medoxomil & Metoprolol Succinate ER Tablets are yellow coloured, round, biconvex, plain on both sides & film coated tablets. The excipients used are Lactose, Microcrystalline Cellulose, Colour Quinoline Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide.

OLSAR M-50

Olmesartan Medoxomil & Metoprolol Succinate ER Tablets are orange coloured, round, biconvex, plain on both sides & film coated tablets. The excipients used are Lactose, Microcrystalline Cellulose, Colour Sunset Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide.

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

OLSAR M are available in Blister strips of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30^{o}C, Protect from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

OLSAR - M

Olmesartan Medoxomil & Metoprolol Succinate ER Tablets

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 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 M tablets are and what they are used for

OLSAR M is combination of Metoprolol Succinate (belongs to a group of medicines called beta blockers.) and Olmesartan Tablets (belong to a group of medicines called angiotensin-II receptor antagonists.) It is used for treatment of essential hypertension.
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.

9.2. What you need to know before you take OLSAR M tablets

Do not take OLSAR M tablets if you:

- are allergic to metoprolol, olmesartan other beta-blockers or any other ingredients of this medicine
- suffer with heart conduction or rhythm problems
- have severe or uncontrolled heart failure
- are in shock caused by heart problems
- suffer with blocked blood vessels, including blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue)
- have a slow heart rate or have suffered a heart attack which has been complicated by a significantly slow heart rate
- suffer from a tight, painful feeling in the chest in periods of rest (Prinzmetal's angina)
- have or have had breathing difficulties or asthma including COPD (Chronic Obstructive Pulmonary Disease
- causing cough, wheezing or breathlessness, phlegm or increase in chest infections)
- suffer with untreated phaeochromocytoma (high blood pressure due to a tumour near the kidney)
- suffer from increased acidity of the blood (metabolic acidosis)

- have low blood pressure
- suffer with diabetes associated with frequent episodes of low blood sugar (hypoglycaemia)
- have liver or kidney disease or failure
- are given other medicines for blood pressure by injection especially verapamil, diltiazem
- If you are more than 3 months pregnant. (It is also better to avoid Olmesartan Tablets in early pregnancy -
- if you suffer from yellowing of the skin and eyes (jaundice) Or problems with drainage of the bile from the gallbladder (biliary obstruction e.g. gallstones).
- if you have diabetes or impaired kidney function and you are Treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor or pharmacist before using OLSAR M tablets if you:
- have a history of allergic reactions, for example to insect stings, foods or other substances,
- have diabetes mellitus (low blood sugar levels may be hidden by this medicine)
- Have controlled heart failure.
- Have a slow heart rate or blood vessel disorder.
- suffer from treated phaeochromocytoma (high blood pressure due to tumour near the kidney)
- have or have suffered from psoriasis (severe skin rashes)
- have liver cirrhosis
- are elderly
- Have myasthenia gravis.
- If you suffer from dry eyes Anaesthetics and surgery

Liver disease

- 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.

If you are going to have an operation or an anaesthetic, please tell your doctor or dentist that you are taking OLSAR M tablets, as your heart beat might slow down too much.
Taking other medicines
Do not take OLSAR M tablets if you are already taking:

- monoamine oxidase inhibitors (MAOIs) for depression
- other blood pressure lowering medicines such as verapamil, nifedipine and diltiazem
- disopyramide or quinidine (to treat irregular heartbeat (arrhythmia)
- An ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
- aliskiren

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.

Children

Do not give this medicine to children.

Other medicine and OLSAR M tablets

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

- medicines used to treat stomach ulcers such as cimetidine
- medicines used to treat high blood pressure such as hydralazine, clonidine or prazosin
- medicines used to treat irregular heart rhythm such as amiodarone and propafenone
- medicines used to treat depression such as tricyclic or SSRI antidepressants
- medicines used to treat epilepsy such as barbiturates
- medicines used to treat mental illness such as phenothiazines
- anaesthetics such as cyclopropane or trichloroethylene
- medicines used to treat some cancers, particularly cancer of the kidney such as aldesleukin
- medicines used to treat erectile dysfunction such as alprostadil
- anxiolytics or hypnotics (e.g. temazepam, nitrazepam, diazepam)
- indometacin or celecoxib [Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)]
- rifampicin (antibiotic) or terbinafine (antifungal)
- oestrogens such as a contraceptive pill or hormone replacement therapy
- corticosteroids (e.g. hydrocortisone, prednisolone)
- Other beta-blockers e.g. eye drops
- adrenaline (epinephrine) or noradrenaline (norepinephrine), used in anaphylactic shock or
- other sympathomimetic
- medicines used to treat diabetes
- lidocaine (a local anaesthetic)
- moxisylyte (used in Raynaud's syndrome)
- medicines used to treat malaria such as mefloquine
- medicines used to prevent nausea and vomiting such as tropisetron
- medicines used to treat asthma such as xanthines such as aminophylline or theophylline
- medicines to treat migraines such as ergotamine
- medicines used to treat heart conditions such as cardiac glycosides e.g. digoxin
- medicines used to treat rheumatoid arthritis such as hydroxychloroquine
- Diphenhydramine (sedative antihistamine)
- 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 Olmesartan 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 Olmesartan Tablets may increase the toxicity of lithium. If you have to take Lithium, your doctor will measure your lithium blood levels. Colesevelam hydrochloride, a drug that lowers the level of cholesterol in your blood, as the effect of Olmesartan may be decreased. Your doctor may advise you to take Olmesartan at least 4 hours before colesevelam hydrochloride
- Certain antacids (indigestion remedies), as the effect of Olmesartan Tablets can be slightly decreased

Older people

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

Black patients
As with other similar drugs the blood pressure lowering effect of Olmesartan Tablets is somewhat less in black patients
OLSAR M tablets and alcohol
You are advised to avoid alcohol whilst taking this medicine. Alcohol may increase the blood pressure lowering effect of OLSAR M tablets.
Pregnancy and breast-feeding
OLSAR M tablets are not recommended during pregnancy or breast-feeding. If you are pregnant or breastfeeding, 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 OLSAR M tablets may make you feel tired and dizzy. If affected, patients should not drive or operate machinery.

9.3. How to take OLSAR M tablets

Always take OLSAR M tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Dosage: As directed by the Physician.
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.
If you take more OLSAR M tablets than you should
If you have accidentally taken more than the prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist at once.
Symptoms of overdose are
low blood pressure (fatigue and dizziness), slow pulse, heart conduction problems, shortness of breath, unconsciousness, coma,, cardiac arrest, feeling and being sick ,blue colouring of the skin, low blood sugar levels and high levels of potassium in the blood.
If you forget to take OLSAR M tablets
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Then go on as before.
Do not take a double dose to make up for a forgotten dose.
If you stop taking OLSAR M tablets
Do not suddenly stop taking OLSAR M tablets as this may cause worsening of heart failure and increase the risk of heart attack. Only change the dose or stop the treatment in consultation with your doctor.
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. Stop treatment and contact a doctor at once if you have the following symptoms of an allergic reaction such as itching, difficulty breathing or swelling of the face, lips, throat or tongue. **Tell your doctor if you notice any of the following side effects or notice any other effects not listed:**
Common (may affect up to 1 in 10 people):

- tiredness
- dizziness
- headache
- a slow heart rate
- feeling faint on standing due to low blood pressure

- shortness of breath with or without strenuous physical activity
- feeling or being sick
- stomach pain
- runny or stuffy nose, Bronchitis, flu-like symptoms, cough,
- Pain, pain in the chest, Back, bones or joints, infection of the urinary tract,
- Swelling of Ankles, feet, legs, hands or arms, blood in the urine.
- Some changes in blood test results have also been seen and Include the following:
- Increased fat levels (hypertriglyceridaemia), increased uric acid levels (hyperuricaemia), rise in blood urea, increases in tests of Liver and muscle function.

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

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

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

- depression
- nightmares
- nervousness
- anxiety
- sexual dysfunction or reduced sex drive
- inability to think clearly
- sleepiness or difficulty in sleeping
- tingling or ‘pins and needles’
- difficulty breathing
- heart failure
- irregular heart rate
- palpitation
- water retention causing swelling
- Raynaud’s phenomenon (causing pain, numbness, coldness and blueness of the fingers)
- diarrhoea or constipation
- skin rash
- muscle cramps
- Lack of energy, 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

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

- changes in the results of blood tests
- effects on blood clotting causing easy or unexplained bruising
- changes in personality
- confusion
- hallucinations
- visual disturbances
- dry or irritated eyes

- ringing in the ears
- loss of hearing with high doses
- heart conduction problems
- chest pain
- gangrene in patients with severe poor circulation
- runny nose
- dry mouth
- weight gain sensitivity to light
- increased sweating
- hair loss
- worsening or new psoriasis
- joint inflammation (arthritis)
- disturbances of sexual desire and performance
- changes in liver function tests
- taste disorders

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

- worsening or development of limping
- hepatitis (symptoms include fever, sickness and yellowing of the skin or whites of the eyes)
- Peyronie's syndrome (bending of the penis)
- symptoms of high levels of the thyroid hormone or low blood sugar may be hidden
- increase in blood fats or decrease in cholesterol
- retroperitoneal fibrosis (symptoms include lower back pain, high blood pressure)
- Occurrence of antinuclear antibodies not associated with systemic lupus erythematosus (SLE).

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 M

Store at a temperature not exceeding 30°C, Protect from light and moisture.

9.6. Contents of the pack and other information

OLSAR - M 25

Each film coated bilayered tablet contains:

Olmesartan Medoxomil I.P….20mg

Metoprolol Tartrate ….25mg

The excipients used are Lactose, Microcrystalline Cellulose, Colour Quinoline Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide. Colours: Quinoline Yellow WS & Titanium dioxide I.P.

OLSAR - M 50

Each film coated bilayered tablet contains:

Olmesartan Medoxomil I.P……20mg

Metoprolol Tartrate ….50mg.

The excipients used are Lactose, Microcrystalline Cellulose, Colour Sunset Yellow, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Crosspovidone, Methocel K100M, Ethy Cellulose, Methylene Chloride, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, HPMC, PEG 6000 and Titanium Dioxide. Colours: Sunset Yellow FCF & Titanium dioxide I.P.

10. Details of manufacturer

Manufactured by:
Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)
Plot No.: 26A-30, Sector-8A, I.I.E.,

SIDCUL, Haridwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No. 31/UA/2013 issued on 01.02.2016

12. Date of revision

JUN 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/OLSAR M 20 & 25/50 mg/JUN-21/02/PI