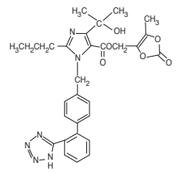
8040722-8883

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

OLMECOR

(Olmesartan medoxomil Tablets 20 mg and 40 mg)

COMPOSITION
OLMECOR
Each film coated tablet contains:
Olmesartan medoxomil….20 mg
OLMECOR
Each film coated tablet contains:
Olmesartan medoxomil….40 mg
DESCRIPTION
Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist.
Olmesartan medoxomil is described chemically as 2,3-dihydroxy-2-butenyl 4(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole5-carboxylate, cyclic 2,3-carbonate.
Its empirical formula is C29H30N6O6 and its structural formula is:



Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol.
CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Pharmaco-therapeutic group: Angiotensin II antagonists, ATC code: C09C A 08.
Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) 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 (AT1) receptor.
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.
PHARMACOKINETICS
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 (Cmax) 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).
Metabolism 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 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 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
Elderly:
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 Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.
INDICATIONS
Treatment of essential hypertension.
CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimesters of pregnancy.
- Biliary obstruction.

WARNINGS AND PRECAUTIONS:
Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue olmesartan as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.
These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of olmesartan as soon as possible.
Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, discontinue olmesartan unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.
Intravascular volume depletion:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of olmesartan medoxomil.
Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.
Renovascular hypertension:
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.
Renal impairment and kidney transplantation:
When olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of olmesartan medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min). There is no experience of the administration of olmesartan medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (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.
The main risk factors for hyperkalaemia to be considered are:
- Diabetes, renal impairment, age (> 70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extended trauma).

Close-monitoring of serum potassium in at risk patients is recommended.
Lithium:
As with other angiotensin-II receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended.
Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.
Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of olmesartan medoxomil is not recommended in such patients.
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.
Effects on Ability to Drive and Use Machines
No studies on the effect on the ability to drive and use machines have been performed. With respect to driving vehicles or operating machines, it should be taken into account that occasionally dizziness or fatigue may occur in patients taking antihypertensive therapy.
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.
Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters). There is no clinical experience with the use of olmesartan in pregnant women.
Lactation
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 Olmetec during breast-feeding, Olmetec is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
SIDE EFFECTS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.
Adult Hypertension
Olmesartan has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year. Treatment with olmesartan was well tolerated, with an incidence of adverse reactions similar to placebo. Events generally were mild, transient and had no relationship to the dose of Olmesartan.
The overall frequency of adverse reactions was not dose-related. Analysis of gender, age and race groups demonstrated no differences between Olmesartan and placebo-treated patients. The rate of withdrawals due to adverse reactions in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with Olmesartan and 2.7% (i.e., 32/1179) of control patients. In placebo-controlled trials, the only adverse reaction that occurred in more than 1% of patients treated with Olmesartan and at a higher incidence versus placebo was dizziness (3% vs. 1%). The following adverse reactions occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with Olmesartan, but also occurred at about the same or greater incidence in patients receiving placebo: back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis.
The incidence of cough was similar in placebo (0.7%) and Olmesartan (0.9%) patients.
Other potentially important adverse reactions that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in the more than 3100 hypertensive patients treated with Olmesartan monotherapy in controlled or open-label trials are listed below.
Body as a Whole: chest pain, peripheral edema
Central and Peripheral Nervous System: vertigo
Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, nausea
Heart Rate and Rhythm Disorders: tachycardia
Metabolic and Nutritional Disorders: hypercholesterolemia, hyperlipemia, hyperuricemia
Musculoskeletal: arthralgia, arthritis, myalgia
Skin and Appendages: rash
Facial edema was reported in five patients receiving Olmesartan. Angioedema has been reported with angiotensin II antagonists.
Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Olmesartan. Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dL and 0.3 volume percent, respectively) were observed.
Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients (0.1%) assigned to Olmesartan and one patient (0.2%) assigned to placebo in clinical trials were withdrawn because of abnormal liver chemistries (transaminases or total bilirubin). Of the five Olmesartan patients, three had elevated transaminases, which were attributed to alcohol use, and one had a single elevated bilirubin value, which normalized while treatment continued.
Pediatric Hypertension
No relevant differences were identified between the adverse experience profile for pediatric patients aged 1 to 16 years and that previously reported for adult patients.
Post-Marketing Experience
The following adverse reactions have been reported in post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Body as a Whole: Asthenia, angioedema
Gastrointestinal: Vomiting
Metabolic and Nutritional Disorders: Hyperkalemia
Musculoskeletal: Rhabdomyolysis
Urogenital System: Acute renal failure, increased blood creatinine levels
Skin and Appendages: Alopecia, pruritus, urticaria
DRUG INTERACTIONS
Interaction studies have only been performed in adults.
Effects of other medicinal products on olmesartan medoxomil:
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.
Other antihypertensive medications:
The blood pressure lowering effect of olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.
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.
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.
DOSAGE AND METHOD OF ADMINISTRATION
Adults
The recommended starting dose of olmesartan medoxomil is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of olmesartan medoxomil may be increased to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, olmesartan medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.
The antihypertensive effect of olmesartan medoxomil 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.
In order to assist compliance, it is recommended that Olmetec tablets be taken at about the same time each day, with or without food, for example at breakfast time.
Elderly
No adjustment of dosage is generally required in elderly patients. 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 olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan medoxomil 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 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, therefore use is not recommended in this patient group. Olmesartan medoxomil should not be used in patients with biliary obstruction.
Children and adolescents
Olmetec is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.
OVERDOSE AND ITS TREATMENT
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.
EXPIRY DATE
Do not use later than the date of expiry.
STORAGE
Store below 30ºC
PRESENTATION
OLMECOR is available in Alu-Alu blister strip of 10 Tablets

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.