OLMESARTAN MEDOXOMIL

℞

OLMETEC®

10 mg, 20 mg and 40 mg Film-coated tablet

1. PHARMACOLOGIC CATEGORY

Angiotensin II Antagonists

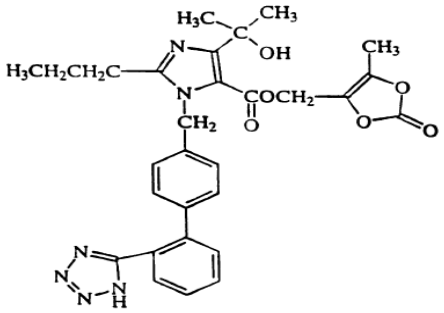
2. DESCRIPTION

Olmesartan medoxomil (Olmetec) 10 mg tablet is a white, circular, film-coated tablets with C13 embossed on one side.
Olmesartan medoxomil (Olmetec) 20 mg tablet is a white, circular, film-coated tablets with C14 embossed on one side.
Olmesartan medoxomil (Olmetec) 40 mg tablet is a white, oval, film-coated tablets with C15 embossed on one side.

Olmesartan medoxomil (Olmetec), a prodrug, which is hydrolyzed to the active metabolite olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Olmesartan medoxomil is described chemically as (5-methyl-2-oxo-1, 3-dioxolen-4-yl) methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1' –biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate. Alternatively, it can be described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate.

Its empirical formula is $C_{29}H_{30}N_6O_6$ and 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.

3. FORMULATION/COMPOSITION

Olmesartan medoxomil (Olmetec) 10 mg Tablet: Each tablet contains 10 mg of Olmesartan medoxomil equivalent to 10 mg of Olmesartan Ph Eur.

Olmesartan medoxomil (Olmetec) 20 mg Tablet: Each tablet contains 20 mg of Olmesartan medoxomil equivalent to 20 mg of Olmesartan Ph Eur.
Olmesartan medoxomil (Olmetec) 40 mg Tablet: Each tablet contains 40 mg of Olmesartan medoxomil equivalent to 40 mg of Olmesartan Ph Eur.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Olmesartan medoxomil (Olmetec) is indicated for the treatment of hypertension.

4.2 Dosage and method of administration

Usual adult dose
The usual recommended dose of olmesartan medoxomil (Olmetec) is in the range 10-40 mg once daily, adjusted according to patient need. If required, further antihypertensive therapy may be used concomitantly with olmesartan medoxomil (Olmetec) to achieve blood pressure control.

Elderly
No initial dosage adjustment is recommended for elderly patients.

Renal impairment
Dosage of olmesartan medoxomil (Olmetec) should be individualized in patients with renal impairment.

There is no experience in the use of olmesartan medoxomil (Olmetec) in patients requiring dialysis.

See Section **4.4 Special warnings and precautions for use** for further information on renal impairment.

Hepatic impairment
No initial dosage adjustment is recommended in patients with mild to moderate hepatic impairment.

Children
The safety and efficacy of olmesartan medoxomil (Olmetec) have not been established in children.

4.3 Contraindications

Olmesartan medoxomil (Olmetec) is contraindicated in patients who are hypersensitive to any component of the tablet, such as microcrystalline cellulose, low substituted hydroxypropylcellulose, lactose, hydroxypropylcellulose and magnesium stearate, talc, titanium dioxide and hypromellose.

Patients who become pregnant should discontinue the use of olmesartan medoxomil (Olmetec) as soon as possible. See Section **4.6 Fertility, pregnancy and lactation** below.

Do not co-administer aliskiren with olmesartan medoxomil (Olmetec) in patients with diabetes (See Section **4.5 Interaction with other medicinal products and other forms of interaction**).

4.4 Special warnings and precautions for use

Pregnancy and lactation
See Section **4.6 Fertility, pregnancy and lactation** regarding use in pregnancy and lactation

Volume- or salt-depleted patients and patients with activated renin-angiotensin system (RAS)
In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients (e.g. those being treated with high doses of diuretics), symptomatic hypotension may occur following the initiation of treatment with olmesartan medoxomil (Olmetec).

Impaired renal function
In patients whose renal function may depend predominantly on the activity of the renin-angiotensin system, treatment with drugs that affect this system has been associated with azotemia, oliguria or, rarely, acute renal failure.

There is an increased risk of 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 system.

Sprue-like Enteropathy
Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan medoxomil (Olmetec) months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan medoxomil (Olmetec), exclude other etiologies. Consider discontinuation of olmesartan medoxomil (Olmetec) in cases where no other etiology is identified.

Electrolyte Imbalance
Olmesartan medoxomil (Olmetec) contains olmesartan, a drug that inhibits the renin-angiotensin system (RAS). Drugs that inhibit the RAS can cause hyperkalemia. Monitor serum electrolytes periodically.

4.5 Interaction with other medicinal products and other forms of interaction

Use with Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including olmesartan. Monitor serum lithium levels during concomitant use.

Dual Blockade of the Renin-Angiotensin System (RAS)
Dual blockade of the RAS with angiotensin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors or aliskiren is associated with increased risks of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared to monotherapy. Monitor blood pressure, renal function and electrolytes in patients on olmesartan and other agents that affect the RAS.

Use with Aliskiren
Do not co-administer aliskiren with olmesartan medoxomil (Olmetec) in patients with diabetes (See Section **4.3 Contraindications**) because dual use is associated with increased risks of

hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)
NSAIDs and angiotensin-receptor blockers (ARBs) may act synergistically by decreasing glomerular filtration. The concomitant use of NSAIDs and ARBs may increase the risk of worsening renal function.

Additionally, the antihypertensive effect of ARBs, including olmesartan, may be attenuated by NSAIDs, including selective cox2 inhibitors.

Use with Colesevelam Hydrochloride
Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect (See Section **5.0 Pharmacological properties**).

4.6 Fertility, pregnancy and lactation

Pregnancy
Use of drugs which act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal injury and even death. Patients who become pregnant while using olmesartan medoxomil should discontinue treatment as soon as possible.

If Olmesartan medoxomil (Olmetec) is used during pregnancy, or if the patient becomes pregnant while taking Olmesartan medoxomil (Olmetec), the patient should be apprised of the potential hazard to a fetus. Should exposure to Olmesartan medoxomil (Olmetec) have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended. Newborns exposed to angiotensin II antagonists *in utero m*ust be closely monitored for the occurrence of hypotension, oliguria, and hyperkalemia.

Lactation
It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug.

4.7 Effects on ability to drive and use machines

No data available

4.8 Undesirable effects

Clinical trial experience
Dizziness has been reported commonly (≥1% <10% incidence) in clinical trials with olmesartan medoxomil (Olmetec).

Post-launch experience
In post launch experience, adverse drug reactions which have been reported very rarely (<0.01% incidence) are: peripheral edema, headache, cough, abdominal pain, nausea,

vomiting, diarrhea, sprue-like enteropathy, anaphylactic reaction, rash, pruritus, angioedema, acute renal failure, hepatic enzymes increased, blood creatinine increased, hyperkalemia, myalgia and asthenic conditions, such as asthenia, fatigue lethargy, malaise.

4.9 Overdose and treatment

Only limited data relevant to overdosage with olmesartan medoxomil (Olmetec) in humans are available. The most likely effect of overdosage is hypotension. In the event of overdosage, treatment should be supportive.

No information is available regarding the dialysability of olmesartan.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore independent of the pathway of angiotensin II synthesis.

Oral doses of olmesartan medoxomil 2.5 to 40 mg inhibited the pressor response to exogenous angiotensin I infusion.

Plasma concentrations of angiotensin I, angiotensin II and plasma renin activity increased after single or repeated administration of olmesartan medoxomil to healthy subjects or hypertensive patients. Olmesartan medoxomil administration had little effect on plasma levels of aldosterone.

In clinical trials in hypertensive patients, olmesartan medoxomil treatment resulted in a dose-dependent reduction in arterial blood pressure. The blood pressure lowering effect of olmesartan medoxomil in a once-daily regimen was maintained throughout the 24-hour dose interval. The efficacy of olmesartan medoxomil, with or without added hydrochlorothiazide as needed, was maintained for up to at least 1 year. There was no evidence of rebound hypertension following interruption of therapy at the 1 year time point.

Olmesartan medoxomil was effective in lowering blood pressure regardless of gender, age or race, although the effect appeared to be somewhat less in black patients (usually a low-renin population).

5.2 Pharmacokinetic properties

Absorption and distribution
Following oral administration, olmesartan medoxomil is rapidly metabolized to its pharmacologically active metabolite, olmesartan. The mean absolute bioavailability of olmesartan from a tablet formulation was found to be about 26%.

The mean peak plasma concentration of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single or repeated oral doses over the therapeutic range.

Food does not affect the bioavailability of olmesartan.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99%). The mean volume of distribution after intravenous dosing is in the range of 16–29 L.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan crossed the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

Metabolism and elimination
Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Approximately 30% to 50% of the systemically absorbed drug is excreted in the urine while the remainder is excreted in feces (via the bile).

Depending on ethnic origin, the terminal elimination half-life of olmesartan varied between 6-15 hours. Steady state was reached after the first few doses and no further accumulation was evident with repeated dosing. Renal clearance was approximately 0.5–0.7 L/h.

Pharmacokinetics in special populations
Elderly:
In Caucasian patients, the AUC at steady state was increased by about 33% in elderly patients. These increases in bioavailability corresponded to reductions in renal clearance of about 30% in elderly.

Renal impairment:
In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min).

The pharmacokinetics of olmesartan in patients undergoing hemodialysis have not been studied.

Hepatic impairment:
Mean olmesartan AUC after single oral administration to patients with moderate hepatic impairment was increased by about 48% compared with healthy controls (total group), or by about 60% when compared with matched controls only.

Interactions
No significant pharmacokinetic interactions were observed in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly affected by antacid (aluminum magnesium hydroxide). Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by these enzymes are not expected.

Drug interaction with 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 (See Section **4.5 Interaction with other medicinal products and other forms of interaction**).

5.3 Preclinical safety data

Preclinical carcinogenicity studies revealed no clinically relevant risk for humans.

In reproductive studies in rats, olmesartan medoxomil did not affect fertility. In common with other angiotensin II receptor antagonists, survival of offspring was reduced following exposure to olmesartan medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats; however, there was no indication of a fetotoxic effect.

5.4 Clinical trials

The Randomized Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study included 4447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor. Patients were randomized to olmesartan 40 mg daily or placebo. The trial met its primary endpoint, delayed-onset of microalbuminuria. For the secondary endpoints, which the study was not designed to formally assess, 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 [0.67%] vs. 3 patients [0.14%] [HR=4.94, 95% CI=1.43-17.06]), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

Please see outer package for the expiry date.

6.2 Storage condition

Store at temperatures not exceeding 30°C.

6.3 Availability

Olmesartan medoxomil (Olmetec) 10 mg tablets: Box of 30’s in blister packs of 10’s.

Olmesartan medoxomil (Olmetec) 20 mg tablets: Box of 30’s in blister packs of 10’s.

Olmesartan medoxomil (Olmetec) 40 mg tablets: Box of 30’s in blister packs of 10’s.

7.0 FDA REGISTRATION NUMBER

10 mg: DRP-3449
20 mg: DRP-3448
40 mg: DRP-3450

8.0 DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

10 mg: 25 August 2004
20 mg: 25 August 2004
40 mg: 25 August 2004

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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