1.0 PHARMACEUTICAL CATEGORY

Antihypertensive
Diuretic

2.0 DESCRIPTION

Olmesartan medoxomil-hydrochlorothiazide is a fixed-dose combination of the angiotensin II (AT\textsubscript{1} subtype) receptor antagonist olmesartan medoxomil and the thiazide diuretic hydrochlorothiazide.

Olmesartan medoxomil

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’-(1\textit{H}-tetrazol-5-yl)-1,1’–biphenyl-4-yl][methyl]-1\textit{H}imidazole-5-carboxylate. Alternatively it can be described as 2,3-dihydroxy-2-butenyl-hydroxy-1-methylethyl)-2-propyl-\{\textit{p}-(o-1\textit{H}-tetrazol-5-ylphenyl)benxyl\}imida carboxylate, cyclic 2,3-carbonate.

Its empirical formula is C\textsubscript{29}H\textsubscript{30}N\textsubscript{6}O\textsubscript{6} and its structural formula is

![Structural formula of Olmesartan Medoxomil](image)

Olmesartan medoxomil is a prodrug which is hydrolyzed during absorption from the gastrointestinal tract to the active metabolite olmesartan.

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol.

Hydrochlorothiazide

Hydrochlorothiazide is described chemically as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1 dioxide.

Hydrochlorothiazide is a white, or practically white, practically odorless powder. It is freely soluble in sodium hydroxide solution, in butylamine, and dimethylformamide; sparingly soluble in methanol; slightly soluble in water; insoluble in ether. In chloroform, and in dilute mineral acids. Its molecular weight is 297.75.
Its empirical formula is C$_7$H$_8$ClN$_3$O$_4$S$_2$ and its structural formula is:

![Structural formula](image)

3.0 FORMULATION

Each Olmetec Plus 20/12.5 mg tablet contains 20 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide

Each Olmetec Plus 40/12.5 mg tablet contains 40 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) fixed dose combination is indicated for use in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or hydrochlorothiazide alone.

4.2 Dosage and Method of Administration

Adults

Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) is administered once daily, with or without food, in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or hydrochlorothiazide alone.

When clinically appropriate, direct change from monotherapy to the fixed combination may be considered. Dose titration of the individual components is recommended.

Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) 20/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide 12.5 or 25 mg monotherapy, or Olmesartan Medoxomil 20mg or Olmesartan Medoxomil 40 mg alone. If additional blood pressure lowering is required the dose may be titrated to the strength of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) 40/12.5 mg.
Elderly

No initial dosage adjustments recommended for elderly patients (see section 5.2 Pharmacokinetic Properties).

Renal impairment

Individualization of therapy within the usual dose regimens of olmesartan medoxomil-hydrochlorothiazide may be used in patients with renal impairment whose creatinine clearance is above 30mL/min. Olmesartan medoxomil-hydrochlorothiazide is not recommended for use in patients with more severe renal disease (creatinine clearance < 30mL/min).

Hepatic impairment

No initial dosage adjustment is necessary in patients with hepatic impairment.

Children and adolescents

The safety and efficacy of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) have not been established in children and adolescents up to 18 years of age.

4.3 Contraindications

Hypersensitivity to Olmesartan medoxomil, Hydrochlorothiazide (or to other sulphonamide-derived substances).

Olmesartan medoxomil-hydrochlorothiazide is contraindicated in patients with anuria, because of the hydrochlorothiazide component.

Patients who become pregnant should discontinue the use of olmesartan medoxomil-hydrochlorothiazide as soon as possible unless no alternative to a drug acting on the renin-angiotensin system can be found.

4.4 Special Warnings and Special Precautions For Use

Intravascular volume depletion:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions should be corrected before the administration of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus).

Impaired renal function:
In patients whose renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), 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.
Thiazide diuretics are not recommended in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia.

**Hepatic impairment:**
Minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

**Metabolic and endocrine effects:**
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required (see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy.

Hyperuricemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

**Electrolyte imbalance:**
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalemia, hyponatremia and hypochloremic alkalosis). Warning signs or symptoms of fluid or electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see section 4.8 Undesirable Effects).

Hypokalemia may develop with the use of thiazide diuretics, especially in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH.

Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

**Lithium:**
As with other medicinal products containing angiotensin II receptor antagonists and thiazide in combination, the coadministration of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) and lithium is not recommended (see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).
Hypersensitivity reactions:
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic lupus erythematosus:
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

4.5 Interaction With Other Drug Products and Other Forms of Interaction

General

Other antihypertensive agents:
The blood pressure lowering effect of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) can be increased by concomitant use of other antihypertensive medications.

Olmesartan medoxomil

No clinically relevant drug interactions with olmesartan medoxomil have been reported to date.

Hydrochlorothiazide

Non-steroidal anti-inflammatory drugs:
The administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Cholestryramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II antagonists. In addition, renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore use of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) and lithium in combination is not recommended (see section 4.4 Special Warnings and Precautions for Use). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Antidiabetic drugs (oral agents and insulin):
Dosage adjustment of the antidiabetic drug may be required (see section 4.4 Special Warnings and Precautions for Use).

Corticosteroids and ACTH:
Patients taking corticosteroids or ACTH are at a greater risk of hypokalemia.

*Pressor amines (eg noradrenaline):*
The effect of pressor amines may be decreased.

*Non-depolarizing skeletal muscle relaxants (eg tubocurarine):*
The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

### 4.6 Pregnancy and Lactation

**Pregnancy**

There is no experience with the use of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) in pregnant women. Studies in mice and rats using olmesartan medoxomil/hydrochlorothiazide combinations do not indicate a teratogenic effect, but fetotoxicity has been shown in rats. Thiazides cross the placental barrier and appear in cord blood. They may cause fetal electrolyte disturbances and possible other reactions that have occurred in adults. Cases of neonatal thrombocytopenia, or fetal or neonatal jaundice have been reported with maternal thiazide therapy.

If pregnancy occurs during therapy, olmesartan medoxomil-hydrochlorothiazide (Olmetec Plus) must be discontinued as soon as possible.

**Lactation**

Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Thiazides appear in human milk. 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

The effect of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) on the ability to drive and use machines has not been specifically studied. However, it should be borne in mind that dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy.

### 4.8 Undesirable effects

**Olmesartan medoxomil-hydrochlorothiazide**

In clinical trials, the overall frequency of adverse events on olmesartan medoxomil/hydrochlorothiazide was similar to that on placebo. The rate of discontinuations due to adverse events on olmesartan medoxomil/hydrochlorothiazide was low (2%) and no higher than on placebo (3%).

Dizziness was reported more frequently on olmesartan medoxomil/hydrochlorothiazide than on placebo.

**Laboratory findings**

In clinical trials, clinically important changes in standard laboratory parameters were rarely associated with olmesartan medoxomil/hydrochlorothiazide.
Minor increases in mean uric acid, blood urea nitrogen and creatinine values and minor decreases in mean hemoglobin and hematocrit values were observed during treatment with olmesartan medoxomil/hydrochlorothiazide.

**Olmesartan medoxomil**

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

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, anaphylactic reaction, rash, pruritus, angio edema, acute renal failure, hepatic enzymes increased, blood creatinine increased, hyperkalemia, myalgia and asthenic conditions such as asthenia, fatigue lethargy, malaise.

**Hydrochlorothiazide**

Adverse events reported with other hydrochlorothiazide preparations are as follows:

*Gastrointestinal system disorders*
Gastric irritation, sialadenitis, pancreatitis

*Hepatobiliary disorders*
Jaundice (intrahepatic cholestatic jaundice)

*Eye disorders*
Xanthopsia, transient blurred vision

*Blood and lymphatic system disorders*
Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia.

*Skin and subcutaneous tissue disorders*
Photosensitivity reactions, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, toxic epidermal necrolysis

*General disorders*
Fever

*Respiratory system disorders*
Respiratory distress (including pneumonitis and pulmonary edema)

*Renal and urinary disorders*
Renal dysfunction, interstitial nephritis

*Musculoskeletal disorders*
Muscle spasm, weakness

*Nervous system disorders*
Restlessness

*Laboratory findings*
Hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance (including hyponatremia and hypokalemia), increases in cholesterol and triglycerides.

4.9 **Overdose**

No specific information is available on the effects or treatment of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) overdosage. Only limited data relevant to overdosage with olmesartan medoxomil in humans are available. The most likely effect of olmesartan overdosage is hypotension. Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, hypochloremia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalemia may accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides. In the event of overdosage with olmesartan medoxomil-hydrochlorothiazide, treatment should be supportive.

No information is available regarding the dialysability of olmesartan or hydrochlorothiazide.

5.0 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

**Olmesartan medoxomil** is a potent, orally active, selective angiotensin II receptor (type AT₁) antagonist. Angiotensin II is the primary 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 AT₁ receptor in vascular smooth muscle. Its action is, therefore independent of the pathway of synthesis of angiotensin II.

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.

**Hydrochlorothiazide** is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of
each component. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension.

5.2 Pharmacokinetic Properties

Concomitant administration of olmesartan medoxomil and hydrochlorothiazide had no clinically-relevant effects on the pharmacokinetics of either component in healthy subjects.

Absorption and Distribution

Olmesartan medoxomil:
Following oral administration, olmesartan medoxomil is rapidly converted 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 (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 or repeated oral doses over the therapeutic range.

Food had no clinically-relevant effect on 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.

Hydrochlorothiazide:
Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing. Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 L/kg.

Metabolism and Elimination

Olmesartan Medoxomil:
Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is actually no further metabolism of olmesartan. Approximately 30% to 50% of the systematically absorbed drug is excreted in the urine whilst the remainder is excreted in feces (via the bile).

Depending on ethnic origin, the terminal elimination half-life of olmesartan varied between 6 and 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.

Hydrochlorothiazide:
Hydrochlorothiazide is not metabolized in man and is excreted almost entirely as unchanged drug in urine. About 60 % of the oral dose is eliminated as unchanged drug within 48 hours. Renal clearance is about 250 – 300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.
Pharmacokinetics in special populations

**Elderly:**
In Caucasian patients, the olmesartan 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 < 20mL/min).

The pharmacokinetics of olmesartan in patients undergoing hemodialysis has 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 (aluminium 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.

### 5.3 Preclinical safety data

The toxic potential of Olmesartan Medoxomil/Hydrochlorothiazide (Olmetec Plus) combinations was evaluated in repeated dose oral toxicity studies for up to six months in rats and dogs. Most observations were due to the pharmacological activity of the combination and there were no findings that would preclude administration to humans at the therapeutic dosage level.

Olmesartan medoxomil/hydrochlorothiazide in a ratio of 20:12.5 was negative in the bacterial reverse mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vivo* Chinese hamster lung chromosomal aberration assay. As expected, a positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio. Olmesartan medoxomil/hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 1935 mg/kg olmesartan medoxomil plus 1209 mg/kg hydrochlorothiazide.
The carcinogenic potential of olmesartan medoxomil and hydrochlorothiazide was not investigated since there was no evidence of relevant carcinogenic effects of the two individual components under conditions relevant to clinical use.

There was no evidence of teratogenicity in mice or rats treated with olmesartan medoxomil/hydrochlorothiazide combinations. As expected with this class of drug, fetal toxicity was observed in rats, as evidenced by significantly reduced fetal body weights, when treated with olmesartan medoxomil/hydrochlorothiazide combinations during gestation.

Studies of the effects of olmesartan medoxomil-hydrochlorothiazide on fertility have not been conducted but studies with the individual components found no adverse effects on fertility in rodents.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf life

See outer package for the expiry date.

6.2 Storage

Store at temperature not exceeding 25°C.

6.3 Availability

Film-coated tablet.

Olmetec Plus 20/12.5 mg tablet: Reddish-yellow, round, film-coated tablet with C22 debossed on one side. Available as blisterpacks of 10’s in boxes of 30’s.

Olmetec Plus 40/12.5 mg tablet: Reddish-yellow, oval, film-coated tablet with C23 debossed on one side. Available as blisterpacks of 10’s in boxes of 30’s.

**CAUTION:** Food, Drugs, Cosmetic and Devices Act prohibits dispensing without prescription.

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