

OLMETEC PLUS® Film-coated tablets SAJA PHARMA

OLMESARTAN MEDOXOMIL / HYDROCHLOROTHIAZIDE

The use of Angiotensin II Receptor antagonists (AIIARs) is not recommended during the first trimester of pregnancy
The use of angiotensin II Receptor antagonists is contraindicated during the 2nd and 3rd trimesters of pregnancy

1. NAME OF THE MEDICINAL PRODUCT

Olmotec Plus 20 mg /12.5 mg film-coated tablets
Olmotec Plus 40 mg/12.5 mg film-coated tablets
Olmotec Plus 40 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olmotec Plus 20 mg /12.5 mg film-coated tablet:
Each film-coated tablet contains 20 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide
Olmotec Plus 40 mg/12.5 mg film-coated tablet:
Each film-coated tablet contains 40 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide.
Olmotec Plus 40 mg/25 mg film-coated tablet:
Each film-coated tablet contains 40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide.

Excipients:

Olmotec Plus 20 mg/12.5 mg film-coated tablet:
Each film-coated tablet contains 110.7 mg lactose monohydrate.

Olmotec Plus 40 mg/12.5 mg film-coated tablet:
Each film-coated tablet contains 233,9 mg lactose monohydrate.

Olmotec Plus 40 mg/25 mg film-coated tablet:
Each film-coated tablet contains 221,4 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

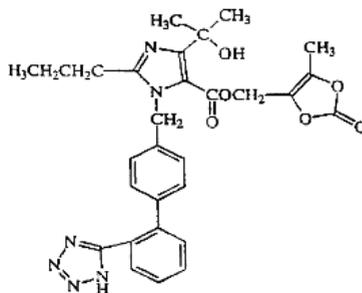
DESCRIPTION

Olmесartan medoxomil-hydrochlorothiazide is fixed-dose combination of the angiotensin II (AT1subtype) 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'-(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.

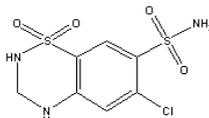
Its empirical formula is $C_{29}H_{30}N_6O_6$ and its structural formula is:



Olmesartan medoxomil is a prodrug which is hydrolysed during absorption from the gastrointestinal tract to the active metabolite olmesartan (see Section 11).

Hydrochlorothiazide

Hydrochlorothiazide is described chemically as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



PHARMACEUTICAL FORM

Olmesartan medoxomil-hydrochlorothiazide is available as film-coated tablets for oral administration in the following strengths:

Olmесartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg

Light Orange, Circular, film-coated tablet with SJ225 debossed on one side.

Olmesartan medoxomil 40 mg plus hydrochlorothiazide 12.5 mg

Light Orange, Biconvex, film-coated tablet with SJ227 debossed on one side.

Olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg

Pinkish, Biconvex, film-coated tablet with SJ231 debossed on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Olmetec Plus is indicated for the treatment of hypertension.

Olmetec Plus is indicated for use in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or hydrochlorothiazide alone.

4.2. Posology and method of administration

Adults

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, taking into account that the antihypertensive effect of olmesartan medoxomil is maximal by about 8 weeks after initiating therapy (see section 5.1).

Dose titration of the individual components is recommended:

20 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide may be administered in patients whose blood pressure is not adequately controlled by the optimal monotherapy olmesartan medoxomil 20 mg alone.

20 mg olmesartan medoxomil/ 25 mg hydrochlorothiazide may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil/ 12.5 mg hydrochlorothiazide.

Olmetec Plus 40 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by olmesartan medoxomil 40 mg alone.

Olmetec Plus 40 mg /25 mg may be administered

in patients whose blood pressure is not adequately controlled on Olmetec Plus 40 mg/12.5 mg fixed dose combination.”

For convenience, patients receiving olmesartan medoxomil and hydrochlorothiazide from separate tablets may be switched to Olmetec Plus tablets containing the same component doses.

Elderly (age 65 years or older)

In elderly patients the same dosage of the combination is recommended as for adults.

Blood pressure should be closely monitored.

Renal impairment

When Olmetec Plus is used in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 ml/min) periodic monitoring of renal function is advised (see section 4.4). Olmetec Plus is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) (see section 4.3).

Hepatic impairment

Olmetec Plus should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.4, 5.2). 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 receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment.

Olmetec Plus should not be used in patients with severe hepatic impairment (see sections 4.3, 5.2), cholestasis and biliary obstruction (see section 4.3).

Paediatric population

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

Method of administration:

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

4.3. Contraindications

Hypersensitivity to the active substances, to any of the excipients (see section 6.1) or to other sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived medicinal product).

Olmesartan / Hydrochlorothiazide should not be co-administered with aliskiren in patients with diabetes mellitus or renal impairment

Severe renal impairment (creatinine clearance <30 mL/min).

Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.

Severe hepatic impairment, cholestasis and biliary obstructive disorders.

2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6).

4.4. Special warnings and precautions for use**Dual Blockade of the Renin-Angiotensin-aldosterone System (RAAS):**

Combination of Olmesartan / Hydrochlorothiazide with ACE inhibitors, or aliskiren may cause increased risks of hyperkalemia, worsening of kidney function and hypotension. Therefore, this combination should not be used, especially in patients with kidney problems.

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 Olmetec Plus.

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 medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

Renovascular hypertension:

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation:

Olmetec Plus should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3). No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance is 30 ml/min, <60 mL/min). However, in such patients Olmetec Plus should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. If progressive renal impairment becomes evident, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy. There is no experience of the administration of Olmetec Plus in patients with a recent kidney transplantation.

Hepatic impairment:

There is currently no experience of olmesartan medoxomil in patients with severe hepatic impairment. Furthermore, minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease. Therefore care should be taken in patients with mild to moderate hepatic impairment (see section 4.2). Use of Olmetec Plus in patients with severe hepatic impairment, cholestasis and biliary obstruction is contraindicated (see sections 4.3, 5.2).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to anti-hypertensive medicinal products

acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmetec Plus is not recommended in such patients.

Metabolic and endocrine effects:

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels are undesirable effects known to be associated with thiazide diuretic therapy.

Hyperuricaemia 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 hypokalaemia, hyponatraemia and hypochloroemic alkalosis). Warning signs of fluid or electrolyte imbalance are 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).

The risk of hypokalaemia is greatest 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 (see section 4.5).

Conversely, due to antagonism at the angiotensin-II receptors (AT₁) through the olmesartan medoxomil component of Olmetec Plus hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels (e.g. heparin)

should be co-administered cautiously with Olmetec Plus (see section 4.5).

There is no evidence that olmesartan medoxomil would reduce or prevent diuretic-induced hyponatraemia. 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. Hypercalcaemia 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 hypomagnesaemia.

Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Lithium:

As with other medicinal products containing angiotensin II receptor antagonists and thiazide in combination, the coadministration of Olmetec Plus and lithium is not recommended (see section 4.5).

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.

Anti-doping test:

Hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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 (see sections 4.3 and 4.6)

Other:

In general arteriosclerosis, in patients with ischaemic heart disease or ischaemic cerebrovascular disease, there is always a risk that excessive blood pressure decrease could result in a myocardial infarction or stroke.

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.

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

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. Interaction with other medicinal products and other forms of interaction

Potential interactions related to both olmesartan medoxomil and hydrochlorothiazide:

Dual RAAS Blockade:

The combination of Olmesartan / Hydrochlorothiazide with Aliskiren, ACEIs or other ARBs is contraindicated in patients with diabetes mellitus or renal impairment.

Dual blockade (e.g. by adding ACE inhibitor to Olmesartan / Hydrochlorothiazide) should not be used, especially in patients with Kidney problems.

Concomitant use not recommended**Lithium:**

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

Concomitant use requiring caution**Baclofen:**

Potential of antihypertensive effect may occur.

Non-steroidal anti-inflammatory medicinal products: NSAIDs (i.e. acetylsalicylic acid (>3g/day), COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of thiazide diuretics and angiotensin II antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of angiotensin II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Concomitant use to be taken into account**Amifostine:**

Potential of antihypertensive effect may occur.

Other antihypertensive agents:

The blood pressure lowering effect of Olmetec Plus can be increased by concomitant use of other antihypertensive medicinal products.

Alcohol, barbiturates, narcotics or antidepressants:

Potential of orthostatic hypotension may occur.

Potential interactions related to olmesartan medoxomil:**Concomitant use not recommended****Medicinal products affecting potassium levels:**

Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE inhibitors) may lead to increases in serum potassium (see section 4.4). If medicinal product which affect potassium levels are to be prescribed in combination with Olmetec Plus, monitoring of potassium plasma levels is advised.

Additional information

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

Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Coadministration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

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

Potential interactions related to hydrochlorothiazide:**Concomitant use not recommended***Medicinal products affecting potassium levels:*

The potassium-depleting effect of hydrochlorothiazide (see section 4.4) may be potentiated by the coadministration of other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended.

Concomitant use requiring caution*Calcium salts:*

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Cholestyramine and colestipol resins:

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Digitalis glycosides:

Thiazide-induced hypokalaemia or hypomagnesaemia

may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances:

Periodic monitoring of serum potassium and ECG is recommended when Olmetec Plus is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulphiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine):

The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic agents (e.g. atropine, biperiden):

Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Antidiabetic medicinal products (oral agents and insulin):

The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4).

Metformin:

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide:

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Pressor amines (e.g. noradrenaline):

The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (probenecid, sulfapyrazone and allopurinol):

Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfapyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine:

Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate):

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates:

In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa:

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine:

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Tetracyclines:

Concomitant administration of tetracyclines and thiazides increases the risk of tetracycline-induced increase in urea. This interaction is probably not applicable to doxycycline.

4.6. Pregnancy and lactation**Pregnancy (see section 4.3):**

Given the effects of the individual components in

this combination product on pregnancy, the use of Olmetec Plus is not recommended during the first trimester of pregnancy (see section 4.4). The use of Olmetec Plus is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Olmesartan medoxomil:

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II antagonists is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

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 2nd and 3rd trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 "Preclinical safety data".)

Should exposure to angiotensin II antagonists have occurred from the 2nd 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 (see also sections 4.3 and 4.4).

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the 2nd and 3rd trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation:

Olmesartan medoxomil:

Because no information is available regarding the use of Olmetec Plus during breastfeeding, Olmetec Plus is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production.

The use of Olmetec Plus during breast feeding is not recommended. If Olmetec Plus is used during breast feeding, doses should be kept as low as possible.

4.7. Effects on ability to drive and use machines

Olmetec Plus can have minor or moderate influence on the ability to drive and use machines. Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react.

4.8. Undesirable effects

a. Summary of the safety profile:

The most commonly reported adverse reactions during treatment with Olmetec Plus are headache (2.9%), dizziness (1.9%) and fatigue (1.0%).

Hydrochlorothiazide may cause or exacerbate vol-

ume depletion which may lead to electrolyte imbalance (see section 4.4).

In clinical trials involving 1155 patients treated with olmesartan medoxomil/hydrochlorothiazide combinations at dosages of 20/12.5 mg or 20/25 mg and 466 patients treated with placebo for periods of up to 21 months, the overall frequency of adverse reactions on olmesartan medoxomil/hydrochlorothiazide combination therapy was similar to that on placebo. Discontinuations due to adverse reactions were also similar for olmesartan medoxomil/hydrochlorothiazide 20/12.5 mg - 20/25 mg (2%) and placebo (3%). The frequency of adverse reactions on olmesartan medoxomil/hydrochlorothiazide overall relative to placebo appeared to be unrelated to age (<65 years versus 65 years), gender or race although the frequency of dizziness was somewhat increased in patients aged >75 years.

In addition, the safety of Olmetec Plus as a high dose combination was investigated in clinical trials in 3709 patients receiving olmesartan medoxomil in combination with hydrochlorothiazide in the dose strengths 40 mg/12.5 mg and 40 mg/25 mg.

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

b. Tabulated list of Adverse reaction:

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

MedDRA System Organ Class			
Adverse reactions	Frequency		
	Olmetec Plus	Olmesartan	HCTZ
Infections and infestations			
Sialadenitis			Rare
Blood and lymphatic system disorders			
Aplastic anaemia			Rare
Bone marrow depression			Rare
Haemolytic anaemia			Rare

Leukopenia			Rare
Neutropenia/ Agranulocytosis			Rare
Thrombocytopenia		Uncommon	Rare
Immune system disorders			
Anaphylactic reactions		Uncommon	Uncommon
Metabolism and nutrition disorders			
Anorexia			Uncommon
Glycosuria			Common
Hypercalcaemia			Common
Hypercholesterolaemia	Uncommon		Very common
Hyperglycaemia			Common
Hyperkalaemia		Rare	
Hypertriglyceridaemia	Uncommon	Common	Very common
Hyperuricaemia	Uncommon	Common	Very common
Hypochloraemia			Common
Hypochloraemic alkalosis			Very rare
Hypokalaemia			Common
Hypomagnesaemia			Common
Hyponatraemia			Common
Hyperamylasaemia			Common
Psychiatric disorders			
Apathy			Rare
Depression			Rare
Restlessness			Rare
Sleep disturbances			Rare
Nervous system disorders			
Confusional state			Common
Convulsions			Rare
Disturbances in consciousness (such as loss of consciousness)	Rare		
Dizziness/light-headedness	Common	Common	Common
Headache	Common	Common	Rare
Loss of appetite			Uncommon
Paraesthesia			Rare
Postural dizziness	Uncommon		
Somnolence	Uncommon		
Syncope	Uncommon		
Eye disorders			
Lacrimation decreased			Rare
Transient blurred vision			Rare
Worsening of pre-existing myopia			Uncommon
Xanthopsia			Rare
Ear and labyrinth disorders			
Vertigo	Uncommon	Uncommon	Rare
Cardiac disorders			
Angina pectoris		Uncommon	
Cardiac arrhythmias			Rare

Palpitations	Uncommon		
Vascular disorders			
Embolism			Rare
Hypotension	Uncommon	Rare	
Necrotising angitis (vasculitis, cutaneous vasculitis)			Rare
Orthostatic hypotension	Uncommon		Uncommon
Thrombosis			Rare
Respiratory, thoracic and mediastinal disorders			
Bronchitis		Common	
Cough	Uncommon	Common	
Dyspnoea			Rare
Interstitial pneumonia			Rare
Pharyngitis		Common	
Pulmonary oedema			Rare
Respiratory distress			Uncommon
Rhinitis		Common	
Gastrointestinal disorders			
Abdominal pain	Uncommon	Common	Common
Constipation			Common
Diarrhoea	Uncommon	Common	Common
Dyspepsia	Uncommon	Common	
Gastric irritation			Common
Gastroenteritis		Common	
Meteorism			Common
Nausea	Uncommon	Common	Common
Pancreatitis			Rare
Paralytic ileus			Very rare
Vomiting	Uncommon	Uncommon	Common
Hepato-biliary disorders			
Acute cholecystitis			Rare
Jaundice (intrahepatic cholestasis icterus)			Rare
Skin and subcutaneous tissue disorders			
Allergic dermatitis		Uncommon	
Anaphylactic skin reactions			Rare
Angioneurotic oedema	Rare	Rare	
Cutaneous lupus erythematoses-like reactions			Rare
Eczema	Uncommon		
Erythema			Uncommon
Exanthem		Uncommon	
Photosensitivity reactions			Uncommon
Puritus		Uncommon	Uncommon
Purpura			Uncommon
Rash	Uncommon	Uncommon	Uncommon
Reactivation of cutaneous lupus erythematoses			Rare
Toxic epidermal necrolysis			Rare
Urticaria	Rare	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders			
Arthralgia	Uncommon		
Arthritis		Common	
Back pain	Uncommon	Common	

Muscle spasm	Uncommon	Rare	
Muscular weakness			Rare
Myalgia	Uncommon	Uncommon	
Pain in extremity	Uncommon		
Paresis			Rare
Skeletal pain		Common	
Renal and urinary disorders			
Acute renal failure	Rare	Rare	
Haematuria	Uncommon	Common	
Interstitial nephritis			Rare
Renal insufficiency		Rare	
Renal dysfunction			Rare
Urinary tract infection		Common	
Reproductive system and breast disorders			
Erectile dysfunction	Uncommon		Uncommon
General disorders and administration site conditions			
Asthenia	Common	Uncommon	
Chest pain	Common	Common	
Face oedema		Uncommon	
Fatigue	Common	Common	
Fever			Rare
Influenza-like symptoms		Common	
Lethargy		Rare	
Malaise	Rare	Uncommon	
Pain		Common	
Peripheral oedema	Common	Common	
Weakness	Uncommon		
Investigations			
Alanine aminotransferase increased	Uncommon		
Aspartate aminotransferase increased	Uncommon		
Blood calcium increased	Uncommon		
Blood creatinine increased	Uncommon	Rare	Common
Blood creatine phosphokinase increased		Common	
Blood glucose increased	Uncommon		
Blood haematocrit decreased	Rare		
Blood haemoglobin decreased	Rare		
Blood lipids increased	Uncommon		
Blood potassium decreased	Uncommon		
Blood potassium increased	Uncommon		
Blood urea increased	Uncommon	Common	Common
Blood urea nitrogen increased	Rare		
Blood uric acid increased	Rare		
Gamma glutamyl transferase increased	Uncommon		
Hepatic enzymes increased		Common	

in temporal association with the intake of angiotensin II receptor blockers.

Post Marketing Experience

Data from one controlled trial and an epidemiologic study have suggested that high-dose olmesartan may increase cardiovascular (CV) risk in diabetic patients, but the overall data are not conclusive. The randomized, placebo-controlled, double-blind ROADMAP trial (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention trial, n=4447) examined the use of olmesartan, 40 mg daily, vs. placebo in patients with type 2 diabetes mellitus, normoalbuminuria, and at least one additional risk factor for CV disease. The trial met its primary endpoint, decrease in time-to-onset of microalbuminuria, but olmesartan had no beneficial effect on decline in glomerular filtration rate (GFR). There was a finding of increased CV mortality (adjudicated sudden cardiac death, fatal myocardial infarction, fatal stroke, revascularization death) in the olmesartan group compared to the placebo group (15 olmesartan vs. 3 placebo, HR 4.9, 95% confidence interval [CI], 1.4, 17), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

The epidemiologic study included patients 65 years and older with overall exposure of >300,000 patient-years. In the sub-group of diabetic patients receiving high-dose olmesartan (40 mg/d) for >6 months, there appeared to be an increased risk of death (HR 2.0, 95% CI 1.1, 3.8) compared to similar patients taking other angiotensin receptor blockers. In contrast, high-dose olmesartan use in non-diabetic patients appeared to be associated with a decreased risk of death (HR 0.46, 95% CI 0.24, 0.86) compared to similar patients taking other angiotensin receptor blockers. No differences were observed between the groups receiving lower doses of olmesartan compared to other angiotensin blockers or those receiving therapy for <6 months.

Overall, these data raise a concern of a possible increased CV risk associated with the use of high-dose olmesartan in diabetic patients. There are, however, concerns with the credibility of the finding of increased CV risk, notably the observation in the

c. Description of selected adverse reaction:

Single cases of rhabdomyolysis have been reported

large epidemiologic study for a survival benefit in non-diabetics of a magnitude similar to the adverse finding in diabetics.

d. Other special population:

Renal impairment and kidney transplantation:

Olmetec Plus should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3). No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance is ≥ 30 ml/min, <60 mL/min). However, in such patients Olmetec Plus should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. If progressive renal impairment becomes evident, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy. There is no experience of the administration of Olmetec Plus in patients with a recent kidney transplantation.

Hepatic impairment:

There is currently no experience of olmesartan medoxomil in patients with severe hepatic impairment. Furthermore, minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease. Therefore care should be taken in patients with mild to moderate hepatic impairment (see section 4.2). Use of Olmetec Plus in patients with severe hepatic impairment, cholestasis and biliary obstruction is contraindicated (see sections 4.3, 5.2).

Elderly (age 65 years or older)

In elderly patients the same dosage of the combination is recommended as for adults.

Blood pressure should be closely monitored.

Paediatric population

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

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 (see sections 4.3 and 4.6)

To reports any side effect(s):

• Saudi Arabia

<ul style="list-style-type: none"> - The National Pharmacovigilance and Drug Safety Centre (NPC) o Fax: +966-11-205-7662 o Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340. o E-mail: npc.drug@sfd.gov.sa o Website: www.sfd.gov.sa/npc

• Other GCC States:

- Please contact the relevant competent authority.
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4.9. Overdose

No specific information is available on the effects or treatment of Olmetec Plus overdose. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of olmesartan medoxomil overdose are expected to be hypotension and tachycardia; bradycardia might also occur. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09D A 08.

Mechanism of action / Pharmacodynamic effects

Olmetec Plus is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Once daily dosing with Olmetec Plus provides an effective and smooth reduction in blood pressure over the 24 hour dose interval.

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

In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

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.

The effect of olmesartan medoxomil on mortality and morbidity is not yet known.

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.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

Clinical efficacy and safety

The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of each component. In pooled placebo-controlled studies, administration of the 20 /12.5 mg and 20 /25 mg combinations of olmesartan medoxomil/hydrochlorothiazide resulted in mean placebo-subtracted systolic/diastolic blood pressure reductions at trough of 12/7 mmHg and 16/9 mmHg, respectively. Age and gender had no clinically relevant effect on response to treatment with olmesartan medoxomil/hydrochlorothiazide combination therapy.

Administration of 12.5 mg and 25 mg hydrochlorothiazide in patients insufficiently controlled by olmesartan medoxomil 20 mg monotherapy gave additional reductions in 24-hour systolic/diastolic blood pressures measured by ambulatory blood pressure monitoring of 7/5 mmHg and 12/7 mmHg, respectively, compared with olmesartan medoxomil monotherapy baseline. The additional mean systolic/diastolic blood pressure reductions at trough compared with baseline, measured conventionally, were 11/10 mmHg and 16/11 mmHg, respectively.

The effectiveness of olmesartan medoxomil/hydrochlorothiazide combination therapy was maintained over long-term (one-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension.

The effects of fixed dose combination of olmesartan medoxomil/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

5.2. Pharmacokinetic properties

Absorption and distribution

Olmesartan medoxomil:

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6%.

The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

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

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound coadministered active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).

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:

Total plasma clearance of olmesartan was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{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 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 (see section 4.3).

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.

Hydrochlorothiazide:

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

Olmetec Plus

The systemic availability of hydrochlorothiazide is reduced by about 20% when co-administered with olmesartan medoxomil, but this modest decrease is not of any clinical relevance. The kinetics of olmesartan are unaffected by the co-administration of hydrochlorothiazide.

Pharmacokinetics in special populations*Elderly (age 65 years or over):*

In hypertensive patients, the olmesartan 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 (see section 4.2).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients compared to young healthy volunteers.

Renal impairment:

In renally impaired patients, the olmesartan AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2, 4.4).

The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

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 (see sections 4.2, 4.4).

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

5.3. Preclinical safety data

The toxic potential of olmesartan medoxomil/hydrochlorothiazide combinations was evaluated in repeated dose oral toxicity studies for up to six months in rats and dogs.

As for each of the individual substances and other medicinal products in this class, the main toxicological target organ of the combination was the kidney. The combination of olmesartan medoxomil/hydrochlorothiazide induced functional renal changes (increases in serum urea nitrogen and in serum creatinine). High dosages caused tubular degeneration and regeneration in the kidneys of rats and dogs, probably via a change in renal haemodynamics (reduced renal perfusion resulting from hypotension with tubular hypoxia and tubular cell degeneration). In addition, the olmesartan medoxomil/hydrochlorothiazide combination caused a decrease in red blood cell parameters (erythrocytes, haemoglobin and haematocrit) and a reduction in heart weight in rats.

These effects have also been observed for other AT_1 receptor antagonists and for ACE inhibitors and they seem to have been induced by the pharmacological action of high dosages of olmesartan medoxomil and seem to be not relevant to humans at the recommended therapeutic doses.

Genotoxicity studies using combined olmesartan medoxomil and hydrochlorothiazide as well as the individual components have not shown any signs of a clinically relevant genotoxic activity.

The carcinogenic potential of a combination of olmesartan medoxomil and hydrochlorothiazide was not investigated as there was no evidence of relevant

carcinogenic effects for the two individual components under conditions of clinical use.

There was no evidence of teratogenicity in mice or rats treated with olmesartan medoxomil/hydrochlorothiazide combinations. As expected from this class of medicinal product, fetal toxicity was observed in rats, as evidenced by significantly reduced fetal body weights, when treated with olmesartan medoxomil/hydrochlorothiazide combinations during gestation (see sections 4.3, 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipient(s)

Hydroxypropylcellulose, magnesium stearate, lactose, low substituted hydroxypropylecellulose, microcrystalline cellulose, opadry yellow 02A22352 for Olemtec Plus 20/12.5 & 40/12.5 or opadry pink 02A24576 for Olmetec plus 40/25

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Forming Aluminum / aluminum blister.

Packs of 28 film-coated tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SAJA Pharmaceuticals

Saudi Arabian Japanese pharmaceutical company limited

Jeddah – Saudi Arabia

Under license from

Daiichi Sankyo Co. Ltd.

Tokyo-Japan

For more information, please contact

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8. MARKETING AUTHORISATION NUMBER(S)

Olmetec plus 20/12.5 mg 40/370/08

Olmetec plus 40/25 mg 42/370/08

Olmetec plus 40/12.5 mg 41/370/08

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14-05-2014

10. DATE OF REVISION OF THE TEXT

Nov 2014