Professional information for OLMETEC PLUS

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OLMETEC PLUS 20/12,5 film-coated tablets

OLMETEC PLUS 20/25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OLMETEC PLUS 20/12,5 film-coated tablet contains 20 mg olmesartan medoxomil and 12,5 mg hydrochlorothiazide.

Each OLMETEC PLUS 20/25 film-coated tablet contains 20 mg olmesartan medoxomil and 25 mg hydrochlorothiazide.

Excipients with known effects:

Each OLMETEC PLUS 20/12,5 film-coated tablet contains sugar (lactose monohydrate): 110,70 mg.

Each OLMETEC PLUS 20/25 film-coated tablet contains sugar (lactose monohydrate): 98,20 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

OLMETEC PLUS 20/12,5: Reddish-yellow, round, film-coated tablet with C22 debossed on one side.

OLMETEC PLUS 20/25: Pinkish, round, film-coated tablet with C24 debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

OLMETEC PLUS is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil alone.

4.2 Posology and method of administration

Posology

Adults

OLMETEC PLUS is administered once daily, with or without food.

A maximum daily dose of OLMETEC PLUS 20/25 should not be exceeded.

OLMETEC PLUS 20/12,5 may be administered in patients whose blood pressure is not adequately controlled by optimal monotherapy of OLMETEC 20 mg alone.

OLMETEC PLUS 20/25 may be administered in patients whose blood pressure is not adequately controlled by OLMETEC PLUS 20/12,5.

Special populations

Elderly

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

Renal impairment

When OLMETEC PLUS is used in patients with mild to moderate renal impairment (creatinine clearance of 30 to 60 mL/min), periodic monitoring of renal function is advised. 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 medicines.

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

Children and adolescents

The safety and efficacy of olmesartan medoxomil have not been established in children and adolescents up to 18 years of age.

Treatment of children up to 18 years is not recommended.

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 or to other sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived medicine), or to any of the ingredients of OLMETEC PLUS (listed in section 6.1).
- Pregnancy and lactation (see sections 4.4 and 4.6).
- Hereditary or idiopathic angioedema.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.

- Renal artery stenosis in patients with a single kidney (see section 4.4).
- Aortic stenosis (see section 4.4).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- The concomitant use of OLMETEC PLUS with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).
- Lithium therapy: Concomitant administration with OLMETEC PLUS may lead to toxic blood concentrations of lithium (see section 4.5).
- Severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.4).
- Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.
- Severe hepatic impairment, cholestasis and biliary obstructive disorders (see section 4.4).
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving OLMETEC PLUS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of OLMETEC PLUS and aliskiren is therefore contraindicated (see section 4.3).

OLMETEC PLUS should not be used concomitantly with aliskiren (see section 4.3).

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Volume and/or sodium depletion should therefore be corrected before the administration of OLMETEC PLUS (see section 4.3).

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system, (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicines that affect this system has been associated with acute hypotension, uraemia, oliguria or acute renal failure (see section 4.3).

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 OLMETEC PLUS (see section 4.3).

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 uraemia (or another kidney disease e.g. 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 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 and 5.2).

Mitral valve stenosis

As with other vasodilators, special caution is indicated in patients suffering from mitral stenosis.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to anti-hypertensive medicines 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 such as in OLMETEC PLUS may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic medicines may be required. 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 such as in OLMETEC PLUS. Hyperuricaemia may occur or an acute gout attack may be precipitated in patients receiving thiazide therapy such as in OLMETEC PLUS.

Electrolyte imbalance

Periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypercalcaemia, hyponatraemia, hypokalaemia and hypochloraemic 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 and oliguria. Tachycardia and gastrointestinal disturbances, such as nausea or vomiting, have also been reported (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 (AT_1) 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 medicines 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.
Hydrochlorothiazide as in OLMETEC PLUS may decrease urinary calcium excretion and cause an intermittant and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Hypercalcaemia may be evidence of hidden hyperparathyroidism. OLMETEC PLUS should be discontinued before carrying out tests for parathyroid function.
Hydrochlorothiazide has been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Sprue-like enteropathy

In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, and in the absence of other apparent etiologies, olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking OLMETEC PLUS should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure,

adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. OLMETEC PLUS should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Acute respiratory toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, OLMETEC PLUS should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Ethnic differences

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 OLMETEC PLUS could produce a positive analytic result in an anti-doping test.

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. 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 receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other

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

Lactose monohydrate

OLMETEC PLUS contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take OLMETEC PLUS.

4.5 Interaction with other medicines and other forms of interaction

Potential interactions related to both olmesartan medoxomil and hydrochlorothiazide contained in OLMETEC PLUS

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with OLMETEC PLUS. 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 4.3).

Concomitant use requiring caution

Baclofen

Potentiation of antihypertensive effect may occur.

Non-steroidal anti-inflammatory drugs

NSAIDs (Nonsteroidal anti-inflammatory drugs) (i.e. acetylsalicylic acid (> 3 g/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 medicines 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

Potentiation of antihypertensive effect may occur.

Other antihypertensive drugs

The blood pressure lowering effect of OLMETEC PLUS can be increased by concomitant use of other antihypertensive medicines.

Alcohol, barbiturates, narcotics or antidepressants

Potentiation of orthostatic hypotension may occur.

Potential interactions related to olmesartan medoxomil

Concomitant use not recommended

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3, 4.4 and 5.1).

Medicines affecting potassium levels

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase serum potassium levels (e.g. heparin, or ACE inhibitors) may lead to increases in serum potassium. If medicines which affect potassium levels are to be prescribed in combination with OLMETEC PLUS, monitoring of potassium plasma levels is advised.

Bile acid sequestering agent colesevelam

Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces $t_{1/2}$. Administration of olmesartan medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering olmesartan medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered (see section 5.2).

Additional information

- After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan medoxomil was observed.
- Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.
- Co-administration 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 medicines metabolised by the above cytochrome P450 enzymes are expected.

Potential interactions related to hydrochlorothiazide

Concomitant use not recommended

Medicines affecting potassium levels

The potassium-depleting effect of hydrochlorothiazide such as in OLMETEC PLUS may be potentiated by the co-administration of other medicines 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.

Colestyramine and colestipol resins

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

Digitalis glycosides (e.g digoxin)

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac dysrhythmias.

Medicines affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when OLMETEC PLUS is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antidysrhythmics); and with the following torsades de pointes (ventricular tachycardia) inducing medicines (including some antidysrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

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

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)

The effect of non-depolarising skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic medicines (e.g. atropine, biperiden)

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

Antidiabetic medicines (oral and insulin)

The treatment with a thiazide such as in OLMETEC PLUS may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicines may be required.

Metformin

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

Beta-blockers and diazoxide

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides such as in OLMETEC PLUS.

Pressor amines (e.g. norepinephrine (noradrenaline))

The effect of pressor amines may be decreased.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medicines may be necessary since hydrochlorothiazide such as in OLMETEC PLUS may raise the level of serum uric acid. An increase in the dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide, such as in OLMETEC PLUS may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine

Thiazides such as in OLMETEC PLUS may increase the risk of adverse effects caused by amantadine.

Cytotoxic medicines (e.g. cyclophosphamide, methotrexate)

Thiazides, such as in OLMETEC PLUS, may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Salicylates

In case of high dosages of salicylates, hydrochlorothiazide such as in OLMETEC PLUS 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 such as in OLMETEC PLUS and methyldopa.

Ciclosporin

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

Tetracyclines

Concomitant administration of tetracyclines and thiazides such as in OLMETEC PLUS increases the risk of tetracycline-induced increase in urea.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

When pregnancy is planned or confirmed, OLMETEC PLUS should be discontinued.

Medicines affecting the renin-angiotensin system such as OLMETEC PLUS, can cause embryonal toxicity, fetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

Olmesartan medoxomil

Exposure to angiotensin II receptor antagonists therapy 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).

Hydrochlorothiazide

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

Lactation

Safety in lactation has not been established (see section 4.3).

OLMETEC PLUS is excreted in breast milk and its effect on the breastfed infant has not been determined. Consequently, mothers on OLMETEC PLUS should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

The effect of 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 occur in patients taking OLMETEC PLUS, which may impair their ability to react.

4.8 Undesirable effects

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

In clinical trials, 1 155 patients were treated with OLMETEC PLUS, at dosages of 20/12,5 mg or 20/25 mg and 466 patients were 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.

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.

Tabulated summary of adverse reactions

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥1/10); common (≥ 1 / 100 to < 1 / 10); uncommon (≥ 1 / 1 000 to, < 1 / 100); rare (≥ 1 / 10 000 to < 1 / 1 000); very rare (< 1 / 10 000), not known (cannot be estimated from the available data).

System organ class	**Frequency**		
	OLMETEC PLUS	**Olmesartan medoxomil**	**Hydrochlorothiazide**
Infections and infestations			
Sialadenitis			Rare
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)			Not known
Blood and lymphatic system disorders			
Thrombocytopenia		Uncommon	Rare
Leucopenia			Rare
Neutropenia / agranulocytosis			Rare
Aplastic anaemia			Rare
Haemolytic anaemia			Rare
Bone marrow			Rare

depression			
Immune system disorders			
Anaphylactic reactions		Uncommon	Uncommon
Metabolism and nutrition disorders			
Hyperuricaemia	Uncommon	Common	Very common
Hyper-triglyceridaemia	Uncommon	Common	Very common
Hypercholesterolaemia	Uncommon		Very common
Hyperkalaemia		Rare	
Hyperglycaemia			Common
Glycosuria			Common
Hyponatraemia			Common
Hypomagnesaemia			Common
Hypochloraemia			Common
Hypokalaemia			Common
Hyperamylasaemia			Common
Hypercalcaemia			Common
Anorexia			Uncommon
Hypochloraemic alcalosis			Very rare
Psychiatric disorders			
Restlessness			Rare
Depression			Rare
Sleep disturbances			Rare
Apathy			Rare
Nervous system disorders			
Dizziness/light-headedness	Common	Common	Common

Headache	Common	Common	Rare
Confusional state			Common
Syncope	Uncommon		
Postural dizziness	Uncommon		
Somnolence	Uncommon		
Loss in consciousness	Rare		
Loss of appetite			Uncommon
Paraesthesia			Rare
Convulsions			Rare
Eye disorders			
Transient blurred vision			Uncommon
Decreased Lacrimation			Uncommon
Worsening of pre-existing myopia			Uncommon
Xanthopsia			Rare
Acute myopia			Not known
Acute angle-closure glaucoma			Not known
Choroidal effusion			Not known
Ear and labyrinth disorders			
Vertigo	Uncommon	Uncommon	Common
Cardiac disorders			
Palpitations	Uncommon		
Angina pectoris		Uncommon	
Cardiac dysrhythmias			Rare
Vascular disorders			
Hypotension	Uncommon	Rare	

Orthostatic hypotension	Uncommon		Uncommon
Necrotising angiitis (vasculitis, cutaneous vasculitis)			Rare
Thrombosis			Rare
Embolism			Rare
Respiratory, thoracic and mediastinal disorders			
Cough	Uncommon	Common	
Bronchitis		Common	
Pharyngitis		Common	
Rhinitis		Common	
Dyspnoea (including interstitial pneumonia and pulmonary oedema)			Rare
Respiratory distress			Uncommon
Acute respiratory distress syndrome (ARDS) (see section 4.4)			Very rare
Gastrointestinal disorders			
Abdominal pain	Uncommon	Common	Common
Nausea	Uncommon	Common	Common
Vomiting	Uncommon	Uncommon	Common
Diarrhoea	Uncommon	Common	Common
Dyspepsia	Uncommon	Common	
Gastric irritation			Common
Meteorism			Common
Constipation			Common

Pancreatitis			Rare
Paralytic ileus			Very rare
Gastroenteritis		Common	
Sprue-like enteropathy (see section 4.4)		Very rare	
Hepatobiliary disorders			
Jaundice (intrahepatic cholestatic icterus)			Rare
Acute cholecystitis.			Rare
Skin and subcutaneous tissue disorders			
Rash	Uncommon	Uncommon	Uncommon
Eczema	Uncommon		
Angioedema	Rare	Rare	
Urticaria	Rare	Uncommon	Uncommon
Pruritus		Uncommon	Uncommon
Exanthema		Uncommon	
Allergic dermatitis		Uncommon	
Face oedema		Uncommon	
Photosensitivity reactions			Uncommon
Cutaneous lupus erythematosus-like reactions			Rare
Reactivation of cutaneous lupus erythematosus			Rare
Anaphylactic skin reactions			Rare

Toxic epidermal necrolysis			Rare
Purpura			Uncommon
Erythema			Uncommon
Musculoskeletal and connective tissue disorders			
Arthralgia	Uncommon		
Back pain	Uncommon	Common	
Myalgia	Uncommon	Uncommon	
Muscle spasm	Uncommon	Rare	
Muscle weakness			Rare
Pain in extremity	Uncommon	Uncommon	
Arthritis		Common	
Skeletal pain		Common	
Paresis			Rare
Renal and urinary disorders			
Acute renal failure	Rare	Rare	
Haematuria	Uncommon	Common	
Urinary tract infection		Common	
Renal insufficiency		Rare	
Renal dysfunction			Rare
Interstitial nephritis			Rare
Reproductive system and breast disorders			
Erectile dysfunction	Uncommon		Uncommon
General disorders and administration site conditions			
Fever			Rare
Fatigue	Common	Common	
Chest pain	Common	Common	

Influenza-like symptoms		Common	
Peripheral oedema	Common	Common	
Pain		Common	
Asthenia	Common	Uncommon	
Weakness	Uncommon		
Malaise	Rare	Uncommon	
Face oedema		Uncommon	
Lethargy		Rare	
Investigations			
Decreased blood potassium	Uncommon		
Increased blood potassium	Uncommon		
Increased blood calcium	Uncommon		
Increased blood urea	Uncommon	Common	Common
Increased blood lipids	Uncommon		
Increased alanine aminotransferase	Uncommon		
Increased aspartate aminotransferase	Uncommon		
Increased gamma glutamyl transferase	Uncommon		
Increased blood glucose	Uncommon		
Increased blood creatinine	Uncommon	Rare	Common
Increased blood creatine phosphokinase		Common	

Increases in mean uric acid values	Rare		
Decreases in mean haemoglobin	Rare		
Decreases in haematocrit values	Rare		
Increased blood urea nitrogen	Rare		
Increased hepatic enzymes		Common	

Description of selected adverse reactions

Additional information on the individual components

Undesirable effects previously reported with either of the individual components may be potential undesirable effects with OLMETEC PLUS, even if not observed in clinical trials with OLMETEC PLUS.

Rhabdomyolysis

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

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of OLMETEC PLUS is important. It allows continued monitoring of the benefit/risk balance of OLMETEC PLUS. Health care providers

are asked to report any suspected adverse reactions to SAHPRA via the “Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the effects or treatment of OLMETEC PLUS overdosage. 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. Activated charcoal may be useful in the treatment of overdosage. 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 overdosage are expected to be hypotension and tachycardia; bradycardia might also occur. Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia; hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac dysrhythmic associated with the concomitant use of digitalis glycosides (e.g. digoxin) or certain antidysrhythmic medicines.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics.

ATC code: C09D A 08.

OLMETEC PLUS is a combination of an angiotensin II receptor blocker (ARB), olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide.

Olmesartan medoxomil

Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT_1) antagonist. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin aldosterone system. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking it's binding to the AT_1 receptor in tissues, including vascular smooth muscle and the adrenal gland. The selective antagonism of the angiotensin II (AT_1) 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 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 reduction in blood pressure over the 24 hour dose interval.

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.

Hydrochlorothiazide

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. 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 to 12 hours.

5.2 Pharmacokinetic properties

Absorption

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.

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.

Distribution

Olmesartan medoxomil

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 co-administered drugs is low (as confirmed by the lack of 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

Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0,83- 1,14 L/kg.

Biotransformation

Olmesartan medoxomil

Total plasma clearance of olmesartan was typically 1,3 L/h (coefficient of variation, 19 %) and was relatively slow compared to hepatic blood flow (approximately 90 L/h).

Following a single oral dose of C^{14}- labelled olmesartan medoxomil, 10 to 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 (approximately 40 %) and hepatobiliary excretion (approximately 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 contra-indicated.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised in man and is excreted almost entirely unchanged in urine. About 60 % of the oral dose is eliminated unchanged within 48 hours. Renal clearance is about 250 to 300 mL/min.

Elimination

Olmesartan medoxomil

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 to 0,7 L/h and was independent of dose.

Hydrochlorothiazide

The terminal elimination half-life of hydrochlorothiazide is 10 to 15 hours. The systemic availability of hydrochlorothiazide is reduced by about 20 % when co-administered with olmesartan medoxomil. The kinetics of olmesartan are unaffected by the co-administration of hydrochlorothiazide.

Special populations

Elderly

In hypertensive, elderly patients (65 to 75 years old), the olmesartan AUC at steady state was increased by approximately 35 % and by approximately 44 % in elderly patients 75 years and older compared with the younger age group.

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.

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 Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment. Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide (see section 4.4).

Drug interactions

Bile acid sequestering agent colesevelam

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28 % reduction in Cmax and 39 % reduction in AUC of olmesartan. Lesser effects, 4 % and 15 % reduction in Cmax and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half-life of olmesartan was reduced by 50 – 52 % irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride (see section 4.5).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

Film coat

OLMETEC PLUS 20/12,5: Opadry O2A22352

OLMETEC PLUS 20/25: Opadry O2A24576

[Opadry O2A22352 & Opadry O2A24576 contains hypromellose, talc, titanium dioxide (E171), iron

(III) oxide yellow (E172), iron (III) oxide red (E172)].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blister in carton until required for use.

6.5 Nature and contents of container

Blister packs comprised of aluminium / aluminium (polyamide/polyvinyl chloride) laminated foil.

Pack size: 14, 28, 30, 56, 84, 90, 98 film-coated tablets or packs of 10 x 28 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville 7551

8. REGISTRATION NUMBER

OLMETEC PLUS 20/12,5: 41/7.1.3/0337

OLMETEC PLUS 20/25: 41/7.1.3/0338

9. DATE OF FIRST AUTHORISATION

18 February 2016

10. DATE OF REVISION OF THE TEXT

13 November 2023