Professional Information for OLMETEC 10, 20 & 40

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OLMETEC 10 film-coated tablets

OLMETEC 20 film-coated tablets

OLMETEC 40 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OLMETEC 10 contains 10 mg olmesartan medoxomil.

OLMETEC 20 contains 20 mg olmesartan medoxomil.

OLMETEC 40 contains 40 mg olmesartan medoxomil.

Excipient with known effect:

Contains sugar:

OLMETEC 10 contains 61,6 mg lactose monohydrate per film-coated tablet.

OLMETEC 20 contains 123,2 mg lactose monohydrate per film-coated tablet.

OLMETEC 40 contains 246,4 mg lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

OLMETEC 10: White circular film-coated tablets with characteristic odour approximately 6,5 mm in diameter, with C13 debossed on one side.

OLMETEC 20 film-coated tablets: White circular film-coated tablets with characteristic odour approximately 8,5 mm in diameter, with C14 debossed on one side.

OLMETEC 40 film-coated tablets: White oval film-coated tablets with characteristic odour approximately 15 x 7 mm in size, with C15 debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension in adults.
- Treatment of hypertension in children and adolescents from 6 to less than 18 years of age.

4.2 Posology and method of administration

Posology

Adults

The recommended starting dose of OLMETEC is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of OLMETEC may be increased to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, OLMETEC dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.

The antihypertensive effect of OLMETEC is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose regimen for any patient.

Elderly patients (65 years or over)

No adjustment of dosage is generally required in elderly people (see below for dose recommendations in patients with renal impairment). If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored.

Renal impairment

The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20 – 60 mL/min) is 20 mg OLMETEC once daily, owing to limited experience of higher dosages in

this patient group. The use of OLMETEC in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended, since there is only limited experience in this patient group (see sections 4.4, 5.2).

Hepatic impairment

No adjustment of dosage recommendations is required for patients with mild hepatic impairment. In patients with moderate hepatic impairment, an initial dose of 10 mg OLMETEC once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive medicines. There is no experience of OLMETEC in patients with severe hepatic impairment, therefore use is not recommended in this patient group (see sections 4.4 and 5.2). OLMETEC should not be used in patients with biliary obstruction (see section 4.3).

Paediatric population

Children and adolescents from 6 to less than 18 years of age:

The recommended starting dose of OLMETEC in children from 6 to less than 18 years of age is 10 mg OLMETEC once daily. In children whose blood pressure is not adequately controlled at this dose, the dose of OLMETEC may be increased to 20 mg once daily. If additional blood pressure reduction is required, in children who weigh ≥ 35 kg, the OLMETEC dose may be increased to a maximum of 40 mg. In children who weigh < 35 kg, the daily dose should not exceed 20 mg.

Other paediatric population

The safety and efficacy of OLMETEC in children aged 1 to 5 years old have not yet been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

OLMETEC should not be used in children aged below 1 year, because of safety concerns and lack of data in this age group.

Method of administration

In order to assist compliance, it is recommended that OLMETEC tablets be taken at about the same time each day, with or without food, for example at breakfast time. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed.

4.3 Contraindications

- Hypersensitivity to olmesartan medoxomil or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Biliary obstruction (see section 5.2).
- The concomitant use of OLMETEC with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of OLMETEC.

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, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated OLMETEC.

Renal impairment and kidney transplantation

When OLMETEC is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of OLMETEC is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min) (see sections 4.2, 5.2). There is no experience of the administration of OLMETEC in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance <12 mL/min).

Hepatic impairment

There is no experience in patients with severe hepatic impairment and therefore use of OLMETEC in this patient group is not recommended (see section 4.2 for dosage recommendations in patients with mild or moderate hepatic impairment).

Hyperkalaemia

The use of medicines that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

The risk, that may be fatal, is increased in elderly people, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicines that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicines that affect the renin-angiotensin- aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered (see also below section “Dual blockade of the renin-angiotensin-aldosterone system (RAAS)”).

The main risk factors for hyperkalaemia to be considered are:

- Diabetes, renal impairment, age (> 70 years)
- Combination with one or more other medicines that affect the renin-angiotensin-aldosterone system and/or potassium supplements.

Some medicines or therapeutic class of medicines may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-inflammatory drugs (NSAIDs) (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim.

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g., acute limb ischaemia, rhabdomyolysis, extended trauma).

Close monitoring of serum potassium in at risk patients is recommended (see section 4.5).

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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

Lithium

The combination of lithium and OLMETEC is not recommended (see section 4.5).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of OLMETEC is not recommended in such patients.

Sprue-like enteropathy

In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking OLMETEC for a few months to years after medicine initiation, possibly caused by a localised delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with OLMETEC, and in the absence of other apparent aetiologies, OLMETEC 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 gastroenterologist) advice should be considered.

Ethnic differences

The blood pressure lowering effect of OLMETEC 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.

Pregnancy

OLMETEC 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 OLMETEC should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other

Excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

OLMETEC contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take OLMETEC.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on OLMETEC

Other antihypertensive medicines

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

ACE inhibitors, angiotensin II receptor blockers 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).

Potassium supplements and potassium-sparing diuretics

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium (see section 4.4). Such concomitant use is therefore not recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (including acetylsalicylic acid at doses > 3 g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment with OLMETEC should be recommended as well as regular hydration of the patient.
Additionally, concomitant treatment can reduce the antihypertensive effect of OLMETEC, leading to their partial loss of efficacy.

Bile acid sequestering medicine colesevelam

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

Other compounds

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of OLMETEC was observed. Coadministration of warfarin and digoxin had no effect on the pharmacokinetic properties of OLMETEC.

Effects of OLMETEC on other medicines

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin-converting enzyme inhibitors and angiotensin II antagonists. Therefore, use of OLMETEC 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.

Other compounds

Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminium hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular OLMETEC had no significant effect on the pharmacokinetic or pharmacodynamic properties of warfarin or the pharmacokinetic properties of digoxin.

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

Paediatric populations

Interaction studies have only been performed in adults.

It is not known if the interactions in children are similar to those in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of OLMETEC is not recommended during the first trimester of pregnancy (see section 4.4). The use of OLMETEC is contraindicated 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 medicines.* 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 OLMETEC should be stopped immediately, and, if appropriate, alternative therapy should be started.

OLMETEC therapy exposure during the second and third 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 OLMETEC have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken OLMETEC should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breastfeeding

OLMETEC is excreted in the milk of lactating rats but it is not known whether OLMETEC is excreted in human milk. Because no information is available regarding the use of OLMETEC during breastfeeding, OLMETEC is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

OLMETEC may impair the ability to drive and use machines. OLMETEC can cause dizziness or fatigue, which may impair the ability to react. Patients experiencing dizziness or fatigue should avoid driving or use of machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment with OLMETEC were headache (7,7 %), influenza-like symptoms (4,0 %), dizziness (3,7 %), hypertriglyceridaemia (2,0 %) and raised creatine phosphokinase (1,3 %).

Tabulated list of adverse reactions

Adverse reactions from OLMETEC in clinical trials, post-authorisation safety studies and spontaneous reporting are summarised in the below table.

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).

MedDRA System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
Immune system disorders	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
Nervous system disorders	Dizziness	Common
	Headache	Common
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	Common
	Pharyngitis	Common
	Cough	Common
	Rhinitis	Common
Gastrointestinal disorders	Gastroenteritis	Common
	Diarrhoea	Common

	Abdominal pain	Common
	Nausea	Common
	Dyspepsia	Common
	Vomiting	Uncommon
	Sprue-like enteropathy (see section 4.4)	Very rare
Skin and subcutaneous tissue disorders	Exanthema	Uncommon
	Allergic dermatitis	Uncommon
	Urticaria	Uncommon
	Rash	Uncommon
	Pruritus	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Arthritis	Common
	Back pain	Common
	Skeletal pain	Common
	Myalgia	Uncommon
	Muscle spasm	Rare
Renal and urinary disorders	Haematuria	Common
	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
General disorders and administration site conditions	Pain	Common
	Chest pain	Common
	Peripheral oedema	Common
	Influenza-like symptoms	Common
	Fatigue	Common
	Face oedema	Uncommon

	Asthenia	Uncommon
	Malaise	Uncommon
	Lethargy	Rare
Investigations	Increased hepatic enzymes	Common
	Increased blood urea	Common
	Increased blood creatine phosphokinase	Common
	Increased blood creatinine	Rare

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

Additional information on special populations

Paediatric population

The safety of OLMETEC was monitored in 361 children and adolescents, aged 1 – 17 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Epistaxis is a common adverse event in children (i.e. ≥ 1/100 to < 1/10) that has not been reported in adults.
- During the 3 weeks of the double-blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6 – 17 years of age in the high OLMETEC dose group.

The overall safety profile for OLMETEC in paediatric patients does not differ significantly from the safety profile in adults.

Elderly patients (age 65 years or over)

In elderly people the frequency of hypotension is slightly increased from rare to uncommon.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of OLMETEC is important. It allows continued monitoring of the benefit/risk balance of OLMETEC. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

The most likely effect of overdosage is hypotension. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of OLMETEC.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists.

ATC code: C09C A 08.

Mechanism of action/pharmacodynamic effects

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT_1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT_1) receptor.

Clinical efficacy and safety

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

Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment. When used together with hydrochlorothiazide, the reduction in blood pressure is additive and coadministration is well tolerated.

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

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4 447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3,2 years, patients received either olmesartan or placebo in addition to other antihypertensive medicines, except ACE inhibitors or ARBs.

Olmesartan significantly reduced the risk in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for blood pressure (BP) differences this risk reduction was no longer statistically significant. Olmesartan was associated with higher rates of cardiovascular mortality and overall mortality. However, olmesartan was not linked with non-fatal strokes, non-fatal myocardial infarction, and non-cardiovascular mortality.

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) investigated the effects of olmesartan on renal and cardiovascular outcomes in 577 randomised Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3,1 years, olmesartan had no effect on renal outcomes (time to first event of the doubling of serum creatinine, end stage renal disease, all-cause death). Olmesartan was associated with higher rates of cardiovascular mortality but not overall mortality, non-fatal strokes, and non-fatal myocardial infarctions.

Paediatric population

The antihypertensive effects of olmesartan medoxomil in the paediatric population were evaluated in a randomised, double-blind, placebo-controlled study in 302 hypertensive patients aged 6 to 17 years. The study population consisted of an all-black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 blacks. The aetiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to < 35 kg were randomised to 2,5 mg (low dose) or 20 mg (high dose) of olmesartan medoxomil once daily and patients who weighed ≥ 35 kg were randomised to 5 mg (low dose) or 40 mg (high dose) of olmesartan medoxomil once daily. Olmesartan medoxomil significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmesartan medoxomil at both low and high doses significantly reduced systolic blood pressure by 6,6 and 11,9 mmHg from the baseline, respectively. The treatment was effective in both, paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥ 5 kg received 0,3 mg/kg of olmesartan medoxomil once daily for three weeks in an open label phase and then were randomised to receiving olmesartan medoxomil or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was

3/3 mm Hg lower in the group randomised to olmesartan medoxomil; this difference in blood pressure was not statistically significant (95 % C.I. -2 to 7/-1 to 7).

Other information

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers.

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death, stroke, hyperkalaemia, hypotension and renal dysfunction were more frequent in the aliskiren group.

5.2 Pharmacokinetic properties

Absorption and distribution

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from

the gastrointestinal tract.

No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25,6 %.

The mean peak plasma concentration (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 pharmacokinetic properties 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 co-administered medicines 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).

Biotransformation and elimination

Total plasma clearance was typically 1,3 L/h (CV, 19 %) and was relatively slow compared to hepatic blood flow (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 (40 %) and hepato-biliary excretion (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.

Pharmacokinetic properties in special populations

Paediatric population

The pharmacokinetic properties of olmesartan were studied in paediatric hypertensive patients aged 1 to 16 years. The clearance of olmesartan in paediatric patients was similar to that in adult patients when adjusted by the body mass.

There is no pharmacokinetic information available in renally impaired paediatric subjects.

Elderly patients (age 65 years or over)

In hypertensive patients, the AUC at steady state was increased by 35 % in elderly people (65 – 75 years old) and by 44 % in very elderly people (≥ 75 years old) compared with the younger age group. This may be at least in part related to a mean decrease in renal function in this group of patients.

Renal impairment

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

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 and 4.4).

Medicine interactions

Bile acid sequestering medicine colesevelam

Concomitant administration of 40 mg olmesartan medoxomil and 3 750 mg colesevelam hydrochloride in healthy subjects resulted in 28 % reduction in C_{max} and 39 % reduction in AUC of olmesartan. Lesser effects, 4 % and 15 % reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. 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).

5.3 Preclinical safety data

In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT_1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT_1 receptors); reduction in heart weight; a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of

olmesartan medoxomil have also occurred in preclinical trials on other AT_1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE inhibitors and other AT_1 receptor antagonists, would appear to have no clinical relevance.

Like other AT_1 receptor antagonists olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures *in vitro*. No relevant effects were observed in several *in vivo* studies using olmesartan medoxomil at very high oral doses of up to 2000 mg/kg. The overall data of a comprehensive genotoxicity testing suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.
Olmesartan medoxomil was not carcinogenic, neither in rats in a 2-year study nor in mice when tested in two 6-month carcinogenicity studies using transgenic models.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropyl cellulose

Lactose monohydrate

Low substituted hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose.

Tablet coating

Hypromellose

Talc

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at or below 30 °C.

6.4 Special precautions for storage

Keep the blister strip in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in a carton containing 10, 14, 28, 30, 50, 56, 84, 90, 98, 280 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Menarini South Africa (Pty) Ltd

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8. REGISTRATION NUMBER

OLMETEC 10: A40/7.1.3/0403

OLMETEC 20: A40/7.1.3/0404

OLMETEC 40: 40/7.1.3/0405

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

OLMETEC 10, 20: 09 October 2009

OLMETEC 40: 15 February 2022

10. DATE OF REVISION OF THE TEXT

To be allocated by the Authority.