OLMETEC™

1. NAME OF THE MEDICINAL PRODUCT

OLMETEC™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg or 40 mg of olmesartan medoxomil.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Olmetec™ 20 mg tablets: White, circular, film-coated tablets with C14 embossed on one side.

Olmetec™ 40 mg tablets: White, oval, film-coated tablets with C15 embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of essential hypertension.

4.2 Posology and method of administration

Adults

The optimal recommended starting dose of olmesartan medoxomil is 20 mg once daily; however, dosage must be individualized. If additional blood pressure reduction is required, olmesartan medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.

For patients with possible depletion of intravascular volume, particularly those with impaired renal function, olmesartan medoxomil should be administered under close medical supervision and consideration should be given to a lower starting dose.

The antihypertensive effect of olmesartan medoxomil 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.

In order to assist compliance, it is recommended that olmesartan medoxomil tablets be taken at about the same time each day, with or without food, for example at breakfast time.

Elderly

No initial dosage adjustment is recommended for elderly patients (see 5.2).
The daily dose in elderly patients should not exceed 20 mg/day.

Renal impairment

The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20-60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan medoxomil 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 5.2).

Hepatic impairment

The use of olmesartan medoxomil is not recommended in patients with hepatic impairment, since there is only limited experience in this patient group (see 4.4, 5.2).

Children and adolescents

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

4.3 Contraindications

Hypersensitivity to the active ingredient or any of the other excipients of olmesartan medoxomil tablets (see 6.1), lactation (see 4.6) and biliary obstruction (see 5.2).

Patient who become pregnant should discontinue the use of olmesartan medoxomil as soon as possible (see 4.6).

Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see 4.5).

4.4 Special warnings and special precautions for use

Intravascular volume depletion:

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

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 drugs 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 with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation:

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

Sprue-like enteropathy:

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

Electrolyte imbalance

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

Hepatic impairment:

There is currently limited experience in patients with mild to moderate hepatic impairment and no experience in patients with severe hepatic impairment, therefore, use of olmesartan medoxomil in these patient groups is not recommended (see 4.2, 5.2).

Hyperkalaemia:

As with other angiotensin II antagonists and angiotensin converting enzyme (ACE) inhibitors, hyperkalaemia may occur during treatment with olmesartan medoxomil, especially in the presence of renal impairment and/or heart failure (see 4.5). Close monitoring of serum potassium levels in at risk patients is recommended.

Lithium:

As with other angiotensin II receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended (see 4.5).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:

As with other vasodilators, 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 drugs acting through inhibition of the rennin-angiotensin system. Therefore, the use of olmesartan medoxomil is not recommended in such patients.

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.

Other:

As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on olmesartan medoxomil:

Potassium supplements and potassium sparing diuretics:

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

Other antihypertensive medications:

The blood pressure lowering effect of olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.

Aliskiren:

Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see 4.3) because dual use is associated with increased risks of hypotension, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses >3 g/day and also selective COX-2 inhibitors) and angiotensin II receptor antagonists may act synergistically by decreasing glomerular filtration. The concomitant use of NSAIDs and angiotensin II antagonists may increase the risk of worsening renal function. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, the antihypertensive effect of angiotensin II antagonists, including olmesartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Colesevelam hydrochloride:

Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect (see 5.2).

Other compounds:

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Co-administration of warfarin and digoxin had no effect on the pharmacokinetics of olmesartan.

Effects of olmesartan medoxomil on other medicinal products:

Lithium:

Reversible increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, including olmesartan. Therefore, use of olmesartan medoxomil and lithium in combination is not recommended (see 4.4). If use of the combination proves necessary, careful monitoring of serum lithium levels during concomitant use is recommended.

Dual blockade of the renin-angiotensin system (RAS):

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

Other compounds:

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

Olmesartan 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, *in vivo* interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

4.6 Pregnancy and lactation

Use in pregnancy (see 4.3):

There is no experience with the use of olmesartan medoxomil in pregnant women. However, drugs that act directly on the rennin-angiotensin system administered during the second and third trimesters

of pregnancy have been reported to cause foetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation, lung hypoplasia, facial abnormalities, limb contracture) and even death.

If pregnancy occurs during therapy, olmesartan medoxomil must be discontinued as soon as possible.

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

Use during lactation (see 4.3):
Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Mothers must not breast-feed if they are taking olmesartan medoxomil.

4.7 Effects on ability to drive and use machines
The effect of olmesartan medoxomil tablets on the ability to drive has not been specifically studied. With respect to driving vehicles or operating machines, it should be taken into account that occasionally dizziness or fatigue may occur in patients taking antihypertensive therapy.

4.8 Undesirable effects
Market experience
The following adverse reactions have been reported in post-marketing experience.
They are listed by System Organ Class and ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000), very rare (<1/10000) including isolated reports.

System Organ Class	Very rare
Blood and lymphatic system disorders	Thrombocytopenia
Nervous system disorders	Dizziness, headache
Respiratory, thoracic and mediastinal	Cough

System Organ Class	Very rare
disorders	
Gastrointestinal disorders	Abdominal pain, nausea, vomiting, diarrhoea, sprue-like enteropathy
Skin and subcutaneous tissue disorders	Pruritus, exanthem, rash Allergic conditions such as angioneurotic oedema, dermatitis allergic, face oedema and urticaria
Musculoskeletal and connective tissue disorders	Muscle cramp, myalgia
Renal and urinary disorders	Acute renal failure and renal insufficiency (see also under Investigations)
General disorders and administration site conditions	Asthenic conditions such as asthenia, fatigue, lethargy, malaise
Investigations	Abnormal renal function tests such as blood creatinine increased and blood urea increased Increased hepatic enzymes
Metabolic and nutritional disorders	Hyperkalaemia
Immune system disorders	Anaphylactic reaction

Clinical trials

In double-blind, placebo-controlled monotherapy studies, the overall incidence of treatment-emergent adverse events was 42.4% on olmesartan medoxomil and 40.9% on placebo.

In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on olmesartan medoxomil and 0.9% on placebo).

In long-term (2-year) treatment, the incidence of withdrawals due to adverse events on olmesartan medoxomil 10 - 20 mg once daily was 3.7%.

The following adverse events have been reported across all clinical trials with olmesartan medoxomil (including trials with active as well as placebo control), irrespective of causality or incidence relative to placebo.

They are listed by body system and ranked under headings of frequency using the conventions described above:

Central nervous system disorders:

Common: Dizziness.

Uncommon: Vertigo.

Cardiovascular disorders:

Rare: Hypotension.

Myo/endo/pericardial and valve disorders:

Uncommon: Angina pectoris.

Respiratory system disorders:

Common: Bronchitis, cough, pharyngitis, rhinitis.

Gastro-intestinal disorders:

Common: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea.

Skin and appendages disorders:

Uncommon: Rash.

Musculoskeletal disorders:

Common: Arthritis, back pain, skeletal pain.

Urinary system disorders:

Common: Haematuria, urinary tract infection.

General disorders:

Common: Chest pain, fatigue, influenza-like symptoms, peripheral oedema, pain.

Laboratory parameters

In placebo-controlled monotherapy studies the incidence was somewhat higher on olmesartan medoxomil compared with placebo for hypertriglyceridaemia (2.0% versus 1.1%) and for raised creatine phosphokinase (1.3% versus 0.7%).

Laboratory adverse events reported across all clinical trials with olmesartan medoxomil (including trials without a placebo control), irrespective of causality or incidence relative to placebo, included:

Metabolic and nutritional disorders:
Common: Increased creatine phosphokinase, hypertriglyceridaemia, hyperuricaemia.
Rare: Hyperkalaemia.

Liver and biliary disorders:
Common: Liver enzyme elevations.

4.9 Overdose

Only limited information is available regarding overdosage in humans. 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 olmesartan.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) 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 rennin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT1) receptor.

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 co-administration is well tolerated.

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

The Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study included 4447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor. Patients were randomised to olmesartan 40 mg daily or placebo. The trial met its primary endpoint, delayed onset of microalbuminuria. For the secondary endpoints, which the study was not designed to formally assess, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients [0.67%] vs. 3 patients [0.14%] [HR=4.94, 95% CI=1.43-17.06]), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

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 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 co-administered drugs 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).

Metabolism and elimination

Total plasma clearance 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 ^{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 (approximately 40%) and hepato-biliary 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 contraindicated (see 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.

Pharmacokinetics in special populations

Elderly:

In hypertensive patients, the AUC at steady state was increased by approximately 35% in elderly patients (65 – 75 years old) and by approximately 44% in very elderly patients ($\geq$75 years old) compared with the younger age group (see 4.2).

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 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. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see 4.2, 4.4).

Interactions

Drug interaction with bile acid sequestering agent colesevelam:

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC, respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride (see 4.5).

5.3 Preclinical safety data

In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT1 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 AT1 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 AT1 receptor antagonists, would appear to have no clinical relevance.

Like other AT1 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 agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats; however, there was no indication of a fetotoxic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Lactose monohydrate

Hydroxypropylcellulose

Magnesium stearate

Tablet coat

Titanium dioxide (E 171)

Talc

Hypromellose

6.2 Shelf-life

Please see details on carton.

6.3 Special precautions for storage

Store below 30°C.

7. MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited

LPD Revision No.: 9

LPD Date: May 22, 2020

Country: Thailand