Cilnidipine and Olmesartan Medoxomil Tablet
Cilnikem OM

1. NAME OF THE MEDICINAL PRODUCT

Cilnikem OM (Cilnidipine, & Olmesartan Medoxomil Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Cilnikem OM

Each film coated tablet contains:

Cilnidipine .....10 mg

Olmesartan Medoxomil IP.....20 mg

Excipients.....q.s.

3. PHARMACEUTICAL FORM

Film coated tablet

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Treatment of essential hypertension.

4.2 Posology and Method of Administration

General Considerations

Dose once daily.

The full blood pressure lowering effects are attained within 2 weeks after a change in dose. It may be taken with or without food.

Replacement Therapy

It may be substituted for its individually titrated components in patients controlled on stable doses of cilnidipine, olmesartan medoxomil taken at the same time.

Add-on/Switch Therapy

Fixed dose combination of cilnidipine, and olmesartan medoxomil may be used to provide additional blood pressure lowering for patients not adequately controlled on maximally tolerated, labeled, or usual doses of any of the following antihypertensive classes: angiotensin receptor blockers (ARB), calcium channel blockers (CCB).

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients. Very limited data are available on the use of this fixed dose combination in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

Renal impairment

The maximum dose of olmesartan medoxomil is 20 mg in patients with mild to moderate renal impairment (creatinine clearance of 30 - 60 mL/min), owing to limited experience of the 40 mg olmesartan medoxomil dosage in this patient group. Monitoring of serum concentrations of potassium and creatinine is advised in patients with moderate renal impairment. The use of fixed dose combination of cilnidipine, olmesartan medoxomil in patients with severe renal impairment (creatinine clearance < 30 mL/min) is contraindicated.

Hepatic impairment

Fixed dose combination of cilnidipine, and olmesartan medoxomil should be used with caution in patients with mild hepatic impairment.

Fixed dose combination of cilnidipine, and olmesartan medoxomil should not be used in patients with severe hepatic impairment, cholestasis or biliary obstruction.

Paediatric population

Fixed dose combination of cilnidipine, and olmesartan medoxomil is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications:

Contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to olmesartan or cilinidipine or any other component of this product.

Second and third trimesters of pregnancy.

Biliary obstruction.

Bilateral renal artery stenosis

The concomitant use of Olmesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2).

Cilnidipine should not be administered in pregnant women and women suspected of being pregnant.

Cardiogenic shock, recent MI or acute unstable angina and severe aortic stenosis.

Cilnidipine should carefully administration in following patients: There is a possibility that the blood concentration raises patients with severe hepatic dysfunction and patients with a history of adverse reactions suffered from calcium antagonist.

Special attention required when administered to patients with serious liver dysfunction because this agent is metabolized in the liver.

4.4 Special Warnings and Special Precautions for Use

Olmesartan

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). There is no experience of the administration of olmesartan medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (ie creatinine clearance <12 mL/min).

Hepatic impairment:

There is no experience in patients with severe hepatic impairment and therefore use of olmesartan medoxomil in this patient group is not recommended.

Hyperkalaemia:

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

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

Before considering the concomitant use of medicinal products 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 medicinal products that affect the renin-angiotensin- aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-inflammatory drugs (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 ischemia, rhabdomyolysis, extended trauma).

Close-monitoring of serum potassium in at risk patients is recommended.

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.

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:

As with other angiotensin-II receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended.

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 renin-angiotensin system. Therefore, the use of Olmesartan medoxomil 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 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, exclude other etiologies. Consider discontinuation of olmesartan medoxomil in cases where no other etiology is identified. In cases where symptoms disappear and sprue-like enteropathy is confirmed by biopsy, treatment with olmesartan medoxomil should not be restarted.

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.

Pregnancy*:*

Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonists therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

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.

Cilnidipine

Sudden withdrawal may exacerbate angina. Discontinue in patients who experience ischemic pain, hypotension, poor cardiac reserve and heart failure following administration. Patient may feel dizziness due to decrease the pressure. So, do not work at height, drive a car or operate heavy machinery while taking this medicine. An ingredient in grapefruit juice may intensify the medicine's effect so avoid drinking grape fruit juice as much as possible.

Administrations of calcium antagonists suddenly stop, the patients develop the symptoms have been reported. Hence, it was reduced gradually and requiring withdrawal of the agent is performed carefully monitored.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Olmesartan

Interaction studies have only been performed in adults.

Effects of other medicinal products on olmesartan medoxomil:

Other antihypertensive medications:

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

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 agent.

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. Such concomitant use is therefore not recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses > 3g/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 should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

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 t1/2. 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.

Other compounds:

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Coadministration 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 toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore use of olmesartan medoxomil and lithium in combination is not recommended. 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 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.

Cilnidipine

Other antihypertensives and antipsychotics that cause hypotension may modify insulin and glucose responses. Quinidine, carbamazepine, phenytoin, rifampicin, cimetidine and erythromycin are also interacted with the Cilnidipine.

4.6 Fertility, Pregnancy and Lactation:

Olmesartan

Pregnancy

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II antagonists is contra-indicated during the 2nd and 3rd trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. *Whilst there is no controlled epidemiological data on the risk with angiotensin II antagonists, similar risks may exist for this class of drugs.* Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Angiotensin II antagonists therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II antagonists should be closely observed for hypotension.

Lactation

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

Cilnidipine

No data available with Cilnidipine in pregnancy and lactation. So this drug should be avoided in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

Olmesartan

Summary of the safety profile:

The most commonly reported adverse reactions during treatment with olmesartan medoxomil are headache (7.7%), influenza-like symptoms (4.0%) and dizziness (3.7%).

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).

The incidence was also 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%).

Tabulated list of adverse reactions:

Adverse reactions from olmesartan medoxomil in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized 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).

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	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	Hepatic enzymes increased	Common
	Blood urea increased	Common
	Blood creatine phosphokinase increased	Common
	Blood creatinine increased	Rare

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

Additional information on special populations

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

Cilnidipine

Skin, skin appendages failure: Desquamation, Quincke's edema, Hair loss, Hives, Pruritus, Erythema multiforme, Papule, Rash, Cutaneous dryness and Drying periocular.

Central-peripheral nervous system disorders: Stiff neck, Stiffness of muscle, Dizziness, Cool feeling, Disorientation, Headache, Sluggishness, Musculus gastrocnemius spasticity, Difficulty walking, Vertigo, Light headedness and Sense to hand vibration.
Impaired vision: Eye abnormalities and Hyperemia, irritation of eyes.
Special sensory impairment of other: Reduced sense of taste and Dysgeusia (bitter).
Mental disorder: Vaguely, Somnolence, Forget things and Insomnia.
Digestive tract disorders: Gastritis, Gastric ulcer, Gastrointestinal hemorrhage, Nausea and vomiting, Diarrhea, Stomatitis, Dry mouth, Gingival hypertrophy, Hemorrhagic gastritis, Brash, Anorexia, Stomach discomfort, Epigastric pain, Constipation, Sense of fullness in the abdomen and Periodontitis.
Liver and bile duct disorders: Liver dysfunction, Hepatocyte damage, Rise of AST, Elevation of ALT and Increase in serum bilirubin.
Metabolism and nutrition disorders: LDH rise, Serum inorganic phosphorus rise, Serum inorganic phosphorus reduction, CPK raise, CPK decline, Serum potassium rise, Decrease in serum potassium, Serum calcium rise, Fasting blood glucose level rise, Blood sugar levels, Serum cholesterol rise, Hyperlipidemia, Blood uric acid increased, Hyponatremia, Serum total protein rise, Urine sugar positive and Triglyceride rise.
Cardiovascular disorders (general): Heart failure, Reduction in blood pressure, ST depression, abnormal electrocardiogram, ST segment elevation, CRP rise, cardiothoracic ratio increase, Myocardial infarction, Heart rate, heart rhythm disorder, Atrioventricular block, Atrial tachycardia, Palpitation, Ventricular tachycardia, Atrial fibrillation, Tachycardia, T-wave inversion, Blood vessels (cardiac) failure, Facial redness, Generalized redness and Transient ischemic stroke.
Respiratory Disorder: Respiratory failure, Pharynx different feeling, Sore throat, Throat burning sensation, Dyspnea, Cough and Epistaxis.
Blood disorder: Red blood cell disorder, Hemoglobin increase, Polycythemia, Anemia Erythropenia, Decreased hemoglobin, Hematocrit value decrease, Hematocrit increase, White blood cell-reticuloendothelial disorder, Variation of eosinophils, Eosinophilia, Leukopenia, Leukocytosis, Changes in neutrophil, Change (rod) neutrophil, Change (segmental) neutrophil, Changes in lymphocyte, Platelet-bleeding coagulopathy, Thrombocytopenia.
Urological disorder: Blood creatinine increased, renal function deterioration, renal failure, Uric protein rise, Urea nitrogen rise, Decrease in urinary volume, frequent urination, Urinary sediment (red blood cells) and Urine sediment (white blood cell).
General: Facial edema, Facial puffiness, Chest pain, Chest distress sense, Tightness of the chest, Bad mood, General malaise (feeling), Edema, glow of the face, Hot flushes, Face heat sensation, Weakness, Lower leg edema, Worsening heart failure, Feeling of warmth. Dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, palpitations, GI disturbances, increased micturition frequency, lethargy, eye pain, depression, ischaemic chest pain, cerebral or myocardial ischaemia, transient blindness, rashes, fever, abnormal liver function, gingival hyperplasia, myalgia, tremor and impotence.

4.9 Overdose

Olmesartan

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

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.

Cilnidipine

Unlike other calcium channel antagonists, cilnidipine blocks the influx of Ca2+ ions into both vascular smooth muscle at the level of L-type Ca2+ channels and neuronal cells at the level of N type Ca2+ channels. The L-type Ca2+ channel blockade by cilnidipine affects predominantly vascular smooth muscle, thereby producing vasodilation of peripheral resistance vessels and coronary arteries. The blockade of N-type Ca2+ channels affects predominantly peripheral nerve endings of sympathetic neurons, thereby dilating blood vessels by lowering plasma catecholamine levels. Cilnidipine produced greater reductions in blood pressure in patients with hypertension than in healthy volunteers. Although increases in heart rate were noted in studies with conventional L-type selective DHPs, the changes in heart rate with cilnidipine were

5.2 Pharmacokinetic Properties

Olmesartan

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 coadministered 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).

Biotransformation and elimination

Total plasma clearance was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10 - 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated.

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

Older people (age 65 years or older):

In hypertensive patients, the AUC at steady state was increased by ca 35% in older people (65 – 75 years old) and by ca 44% in very old 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.

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.

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 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

Cilnidipine

After oral administration, large amount of the drug could be detected in the gallbladder, bladder, liver and kidney. Approximately 18 %-29 % and 80 % of the dose was excreted in urine and feces, respectively within 72 h in dogs. The purpose of this experiment was to investigate the metabolism of cilnidipine in human liver microsomes in vitro and the effects of selective CYP450 inhibitors on the metabolism of cilnidipine in human liver microsomes and the major CYP450 isoform involved in the metabolism of cilnidipine.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life
24 months

6.2 Special Precautions for Storage
Store below 30^0C.
Protect from light.
Keep out of reach of children.

6.3 Nature and Contents of Container
10 X 10 tablets

7. MARKETED BY
Alkem Laboratories Ltd.
ALKEM HOUSE,
S. B. Road, Lower Parel (West),
Mumbai- 400 013.

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