Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Olmesartan Hydrochlorothiazide Rowex 40 mg/25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide.

Excipients with known effect
Each film-coated tablet contains 278.2 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow film coated, oval shape, biconvex tablets debossed with 'L348' on one side and plain on other side.
Dimension: 16mm x 7.5mm

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg fixed dose combinations are indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil 40 mg alone.

4.2 Posology and method of administration

Posology

Adults
The recommended dose of Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg or 40 mg/25 mg is 1 tablet per day.

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

Olmesartan Hydrochlorothiazide Rowex 40 mg /25 mg may be administered in patients whose blood pressure is not adequately controlled on Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg fixed dose combination.

For convenience, patients receiving olmesartan medoxomil and hydrochlorothiazide from separate tablets may be switched to Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg tablets containing the same component doses.

Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg can be taken with or without food.

Elderly (age 65 years or over)
In elderly patients the same dosage of the combination is recommended as for adults.
Blood pressure should be closely monitored.

Renal impairment
Olmesartan medoxomil/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min).

The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group, and periodic monitoring is advised.
Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg are therefore contraindicated in all stages of renal impairment (see sections 4.3, 4.4, 5.2).

Hepatic impairment
Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg should be used with caution in patients with mild hepatic impairment (see sections 4.4, 5.2). Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are receiving diuretics and/or other antihypertensive agents. In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment. Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg therefore should not be used in patients with moderate and severe hepatic impairment (see sections 4.3, 5.2), as well as in cholestasis and biliary obstruction (see section 4.3).

Paediatric population
The safety and efficacy of Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg in children and adolescents below 18 years has not been established. No data are available.

Method of administration
Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg can be taken with or without food.
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time each day.

4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients listed in section 6.1 or to other sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived medicinal product).
- Renal impairment (see sections 4.4 and 5.2).
- Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.
- Moderate and severe hepatic impairment, cholestasis and biliary obstructive disorders (see section 5.2).
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Olmesartan Hydrochlorothiazide Rowex with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (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 Olmesartan Hydrochlorothiazide Rowex.

Other conditions with stimulation of the renin-angiotensin-aldosterone system
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

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.

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
Olmesartan medoxomil/hydrochlorothiazide should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min).

The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min) is 20 mg olmesartan medoxomil once daily. However, in such patients olmesartan medoxomil/hydrochlorothiazide 20 mg/12.5 mg and 20 mg/25 mg should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. If progressive renal impairment becomes evident, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg is therefore contraindicated in all stages of renal impairment (see section 4.3).

There is no experience of the administration of olmesartan medoxomil/hydrochlorothiazide in patients with a recent kidney transplantation.

Hepatic impairment
There is currently no experience of olmesartan medoxomil in patients with severe hepatic impairment. In patients with moderate hepatic impairment, the maximum dose is 20 mg olmesartan medoxomil.

Furthermore, minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Therefore the use of Olmesartan Hydrochlorothiazide Rowex 40 mg/12.5 mg and 40 mg/25 mg in patients with moderate and severe hepatic impairment, cholestasis and biliary obstruction is contraindicated (see sections 4.3, 5.2). Care should be taken in patients with mild impairment (see section 4.2).

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

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to anti-hypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmesartan Hydrochlorothiazide Rowex is not recommended in such patients.

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

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

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see section 4.8).

The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Conversely, due to antagonism at the angiotensin-II receptors (AT_1) through the olmesartan medoxomil component of Olmesartan Hydrochlorothiazide Rowex hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels (e.g. heparin) should be coadministered cautiously with Olmesartan Hydrochlorothiazide Rowex (see section 4.5).

There is no evidence that olmesartan medoxomil would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Dilutional hyponatraemia may occur in oedematous patients in hot weather.

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

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Lithium
As with other angiotensin II receptor antagonists, the coadministration of Olmesartan Hydrochlorothiazide Rowex and lithium is not recommended (see section 4.5).

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 medicinal product initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, and in the absence of other apparent etiologies, olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.

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

Ethnic differences
As with all other angiotensin II receptor antagonist containing products, the blood pressure lowering effect of Olmesartan Hydrochlorothiazide Rowex is somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

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

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

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.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interactions

Potential interactions related to olmesartan medoxomil and hydrochlorothiazide
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II receptor antagonists. In addition, renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore use of Olmesartan Hydrochlorothiazide Rowex and lithium in combination is not recommended (see section 4.4). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Baclofen
Potentiation of antihypertensive effect may occur.

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

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

Concomitant use to be taken into account
Amifostine
Potentiation of antihypertensive effect may occur.

Other antihypertensive agents
The blood pressure lowering effect of Olmesartan Hydrochlorothiazide Rowex can be increased by concomitant use of other antihypertensive medicinal products.

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Potential interactions related to olmesartan medoxomil:

Concomitant use not recommended

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 (see sections 4.3, 4.4 and 5.1).

Medicinal products affecting potassium levels

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

Bile acid sequestering agent colesevelam

Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces 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 (see section 5.2).

Additional information

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

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

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

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

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 (see sections 4.3, 4.4 and 5.1).

Potential interactions related to hydrochlorothiazide:

Concomitant use not recommended

Medicinal products affecting potassium levels

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

Concomitant use requiring caution

Calcium salts

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

Cholestyramine and colestipol resins

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

Digitalis glycosides

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

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Olmesartan Hydrochlorothiazide Rowex is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):
- Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine)
The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

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

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

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

Pressor amines (e.g. noradrenaline)
The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

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

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Given the effects of the individual components in this combination product on pregnancy, the use of Olmesartan Hydrochlorothiazide Rowex is not recommended during the first trimester of pregnancy (see section 4.4). The use of Olmesartan Hydrochlorothiazide Rowex is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Olmesartan medoxomil

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

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

Exposure to angiotensin II receptor antagonists therapy during the 2nd and 3rd trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also section 5.3).

Should exposure to angiotensin II receptor antagonists have occurred from the 2nd trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see also sections 4.3 and 4.4).

Hydrochlorothiazide

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

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

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

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

Breast-feeding

Olmesartan medoxomil

Because no information is available regarding the use of Olmesartan Hydrochlorothiazide Rowex during breast-feeding, Olmesartan Hydrochlorothiazide Rowex is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide

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

The use of Olmesartan Hydrochlorothiazide Rowex during breast-feeding is not recommended. If Olmesartan Hydrochlorothiazide Rowex is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported adverse reactions during treatment with olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg and 40 mg/25 mg are headache (2.9%), dizziness (1.9%) and fatigue (1.0%).

Hydrochlorothiazide may cause or exacerbate volume depletion which may lead to electrolyte imbalance (see section 4.4).

The safety of olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg and 40 mg/25 mg was investigated in clinical trials in 3709 patients receiving olmesartan medoxomil in combination with hydrochlorothiazide.

Further adverse reactions reported with the fixed dose combination of olmesartan medoxomil and hydrochlorothiazide in the lower dose strengths 20 mg/12.5 mg and 20 mg/25 mg may be potential adverse reactions with olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg and 40 mg/25 mg.

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

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**		
		Olmesartan/HCT	**Olmesartan**	**HCT**
Infections and infestations	Sialadenitis			Rare
Blood and lymphatic system disorders	Aplastic anaemia			Rare
	Bone marrow depression			Rare
	Haemolytic anaemia			Rare
	Leukopenia			Rare
	Neutropenia/ Agranulocytosis			Rare
	Thrombocytopenia		Uncommon	Rare
Immune system disorders	Anaphylactic reactions		Uncommon	Uncommon
Metabolism and nutrition disorders	Anorexia			Uncommon
	Glykosuria			Common
	Hypercalcaemia			Common
	Hypercholesterolaemia	Uncommon		Very common
	Hyperglycaemia			Common
	Hyperkalaemia		Rare	
	Hypertriglyceridaemia	Uncommon	Common	Very common
	Hyperuricaemia	Uncommon	Common	Very common
	Hypochloraemia			Common
	Hypochloraemic alcalosis			Very rare
	Hypokaliaemia			Common
	Hypomagnesaemia			Common
	Hyponatriaemia			Common
	Hyperamylasaemia			Common
Psychiatric disorders	Apathy			Rare
	Depression			Rare
	Restlessness			Rare
	Sleep disturbances			Rare
Nervous system disorders	Confusional state			Common
	Convulsions			Rare
	Disturbances in consciousness (such as loss of	Rare		

	consciousness)			
	Dizziness/light-headedness	Common	Common	Common
	Headache	Common	Common	Rare
	Loss of appetite			Uncommon
	Paraesthesia			Rare
	Postural dizziness	Uncommon		
	Somnolence	Uncommon		
	Syncope	Uncommon		
Eye disorders	Lacrimation decreased			Rare
	Transient blurred vision			Rare
	Worsening of pre-existing myopia			Uncommon
	Acute myopia, acute angle-closure glaucoma, choroidal effusion			Not known
	Xanthopsia			Rare
Ear and labyrinth disorders	Vertigo	Uncommon	Uncommon	Rare
Cardiac disorders	Angina pectoris		Uncommon	
	Cardiac arrhythmias			Rare
	Palpitations	Uncommon		
Vascular disorders	Embolism			Rare
	Hypotension	Uncommon	Rare	
	Necrotising angiitis (vasculitis, cutaneous vasculitis)			Rare
	Orthostatic hypotension	Uncommon		Uncommon
	Thrombosis			Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis		Common	
	Cough	Uncommon	Common	
	Dyspnoea			Rare
	Interstitial pneumonia			Rare
	Pharyngitis		Common	
	Pulmonary oedema			Rare
	Respiratory distress			Uncommon
	Rhinitis		Common	
Gastrointestinal disorders	Abdominal pain	Uncommon	Common	Common
	Constipation			Common
	Diarrhoea	Uncommon	Common	Common
	Dyspepsia	Uncommon	Common	
	Gastric irritation			Common
	Gastroenteritis		Common	
	Meteorism			Common
	Nausea	Uncommon	Common	Common
	Pancreatitis			Rare
	Paralytic ileus			Very rare
	Vomiting	Uncommon	Uncommon	Common
	Sprue-like enteropathy (see section 4.4)		Very rare	
Hepatobiliary disorders	Acute cholecystitis			Rare
	Jaundice (intrahepatic cholestasic icterus)			Rare
Skin and subcutaneous tissue disorders	Allergic dermatitis		Uncommon	
	Anaphylactic skin reactions			Rare
	Angioneurotic oedema	Rare	Rare	
	Cutaneous lupus erythematodes-like reactions			Rare
	Eczema	Uncommon		
	Erythema			Uncommon
	Exanthem		Uncommon	
	Photosensitivity reactions			Uncommon
	Pruritus		Uncommon	Uncommon
	Purpura			Uncommon

	Rash	Uncommon	Uncommon	Uncommon
	Reactivation of cutaneous lupus erythematodes			Rare
	Toxic epidermal necrolysis			Rare
	Urticaria	Rare	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon		
	Arthritis		Common	
	Back pain	Uncommon	Common	
	Muscle spasm	Uncommon	Rare	
	Muscular weakness			Rare
	Myalgia	Uncommon	Uncommon	
	Pain in extremity	Uncommon		
	Paresis			Rare
	Skeletal pain		Common	
Renal and urinary disorders	Acute renal failure	Rare	Rare	
	Haematuria	Uncommon	Common	
	Interstitial nephritis			Rare
	Renal insufficiency		Rare	
	Renal dysfunction			Rare
	Urinary tract infection		Common	
Reproductive system and breast disorders	Erectile dysfunction	Uncommon		Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)*			Not known
General disorders and administration site conditions	Asthenia	Common	Uncommon	
	Chest pain	Common	Common	
	Face oedema		Uncommon	
	Fatigue	Common	Common	
	Fever			Rare
	Influenza-like symptoms		Common	
	Lethargy		Rare	
	Malaise	Rare	Uncommon	
	Pain		Common	
	Peripheral oedema	Common	Common	
	Weakness	Uncommon		
Investigations	Alanine aminotransferase increased	Uncommon		
	Aspartate aminotransferase increased	Uncommon		
	Blood calcium increased	Uncommon		
	Blood creatinine increased	Uncommon	Rare	Common
	Blood creatine phosphokinase increased		Common	
	Blood glucose increased	Uncommon		
	Blood haematocrit decreased	Rare		
	Blood haemoglobin decreased	Rare		
	Blood lipids increased	Uncommon		
	Blood potassium decreased	Uncommon		
	Blood potassium increased	Uncommon		
	Blood urea increased	Uncommon	Common	Common
	Blood urea nitrogen increased	Rare		
	Blood uric acid increased	Rare		
	Gamma glutamyl transferase increased	Uncommon		
	Hepatic enzymes increased		Common	

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

*Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie

4.9 Overdose

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiontension system, Angiotensin II antagonists and diuretics, ATC code: C09DA08.

Mechanism of action / Pharmacodynamic effects
Olmesartan Hydrochlorothiazide Rowex is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Once daily dosing with olmesartan medoxomil/hydrochlorothiazide provides an effective and smooth reduction in blood pressure over the 24 hour dose interval.

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

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

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

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment.

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

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 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 agents, except ACE inhibitors or ARBs.
For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2% (178 of 2160) of the patients in the olmesartan group and 9.8% (210 of 2139) in the placebo group developed microalbuminuria.
For the secondary endpoints, 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 (0.7%) vs. 3 patients (0.1%)), despite similar rates for non-fatal stroke (14 patients (0.6%) vs. 8 patients (0.4%)), non-fatal myocardial infarction (17 patients (0.8%) vs. 26 patients (1.2%)) and non-cardiovascular mortality (11 patients (0.5%) vs. 12 patients (0.5%)). Overall mortality with olmesartan was numerically increased (26 patients (1.2%) vs. 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events.

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 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3.1 years, patients received either olmesartan or placebo in addition to other antihypertensive agents including ACE inhibitors.
The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all-cause death) occurred in 116 patients in the olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (HR 0.97 (95% CI 0.75 to 1.24); p=0.791). The composite secondary cardiovascular endpoint occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5%) patients receiving olmesartan versus 3 (1.1%) receiving placebo, overall mortality 19 (6.7%) versus 20 (7.0%), non-fatal stroke 8 (2.8%) versus 11 (3.9%) and non-fatal myocardial infarction 3 (1.1%) versus 7 (2.5%), respectively.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

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

Clinical efficacy and safety
The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of each component.

In pooled placebo-controlled studies, administration of the 20 mg /12.5 mg and 20 mg /25 mg combinations of olmesartan medoxomil/hydrochlorothiazide resulted in mean placebo-subtracted systolic/diastolic blood pressure reductions at trough of 12/7 mm Hg and 16/9 mm Hg, respectively.

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

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

The fixed combinations of olmesartan medoxomil and hydrochlorothiazide 40 mg/12.5 mg and 40 mg/25 mg were investigated in three clinical studies including 1482 hypertensive patients.

A double-blind study with essential hypertension evaluated the effectiveness of Olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg combination therapy versus olmesartan medoxomil monotherapy 40 mg with mean sitting diastolic blood pressure reduction being the primary efficacy parameter. Systolic/diastolic blood pressure was reduced by 31.9/18.9 mmHg in the combination group as compared to 26.5/15.8 in the monotherapy group ($p<0.0001$) after 8 weeks of treatment.

In a double-blind but non-controlled second phase of this study, up-titration of non-responders from olmesartan medoxomil monotherapy 40 mg to Olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg as well as from Olmesartan medoxomil/hydrochlorothiazide 40 mg/12.5 mg to Olmesartan medoxomil/hydrochlorothiazide 40 mg/25 mg resulted in a further relevant decrease in systolic/diastolic blood pressure, thus confirming that up-titration is a clinically meaningful way to improve blood pressure control.

A second double-blind, randomised, placebo-controlled study evaluated the effectiveness of adding hydrochlorothiazide to the treatment of patients not adequately controlled after 8 weeks of treatment with Olmesartan medoxomil 40 mg. Patients either continued on Olmesartan medoxomil 40 mg or received additional hydrochlorothiazide 12.5mg or 25mg respectively for another 8 weeks. A fourth group was randomised to receive Olmesartan medoxomil/hydrochlorothiazide 20 mg/12.5 mg.

Adding hydrochlorothiazide 12.5 mg or 25 mg resulted in a further reduction in systolic/diastolic blood pressure of 5.2/3.4 mmHg ($p < 0.0001$) and 7.4/5.3 mmHg ($p < 0.0001$) respectively as compared to the Olmesartan medoxomil 40 mg therapy alone.

A comparison between patients receiving Olmesartan medoxomil/hydrochlorothiazide 20 mg/12.5 mg and patients receiving 40 mg/12.5 mg showed a statistical significant difference in systolic blood pressure reduction of 2.6 mmHg in favour of the higher dose combination ($p=0.0255$) whereas for diastolic blood pressure reduction a difference of 0.9 mmHg was observed. Ambulatory blood pressure monitoring (ABPM) based on the mean changes on 24-hour, daytime and night-time diastolic and systolic blood pressure data confirmed the results of conventional blood pressure measures.

Another double-blind, randomised trial compared the effectiveness of a combination treatment with Olmesartan medoxomil/hydrochlorothiazide 20 mg/25 mg and Olmesartan medoxomil/hydrochlorothiazide 40 mg/25 mg in patients with inadequately controlled blood pressure after 8 weeks of treatment with Olmesartan medoxomil 40 mg.

After 8 weeks of combination therapy the systolic/diastolic blood pressure was significantly reduced as compared to baseline by 17.1/10.5 mmHg in the Olmesartan medoxomil/hydrochlorothiazide 20 mg/25 mg group and 17.4/11.2 mmHg in the Olmesartan medoxomil/hydrochlorothiazide 40 mg/25 mg group. The difference between both treatment groups was not statistically significant when using conventional blood pressure measurement, which might be explained by the known flat dose response effect of angiotensin II receptor antagonists such as Olmesartan medoxomil.
However, a clinically meaningful and statistically significant difference in favour of Olmesartan medoxomil/hydrochlorothiazide 40 mg/25 mg as compared to Olmesartan medoxomil/hydrochlorothiazide 20 mg/25 mg was observed in mean 24-hour, daytime and night-time ABPM on both systolic and diastolic blood pressure.

The antihypertensive effect of Olmesartan medoxomil/hydrochlorothiazide was similar irrespective of age, gender or diabetes status.
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 and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Absorption and distribution

Olmesartan medoxomil

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

The mean peak plasma concentration (Cmax) 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 active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).

Hydrochlorothiazide

Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing. Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 L/kg.

Biotransformation and elimination

Olmesartan medoxomil

Total plasma clearance of olmesartan was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of 14C-labelled olmesartan medoxomil, 10 - 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

The terminal elimination half life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 – 0.7 L/h and was independent of dose.

Hydrochlorothiazide

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

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

Pharmacokinetics in special populations
Elderly (age 65 years or over):
In hypertensive patients, the olmesartan AUC at steady state was increased by ca 35% in elderly patients (65 – 75 years old) and by ca 44% in very elderly patients (≥ 75 years old) compared with the younger age group (see section 4.2).

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

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

The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min) is 20 mg olmesartan medoxomil once daily. The use of olmesartan medoxomil in patients with severe renal impairment (creatinine clearance of < 30 mL/min) is not recommended.

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

Hepatic impairment
After single oral administration, olmesartan AUC values were 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC was again about 65% higher than in matched healthy controls. Olmesartan mean Cmax values were similar in hepatically impaired and healthy subjects.

In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2, 4.3, 4.4).

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide**.**

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

5.3 Preclinical safety data

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

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

caused a decrease in red blood cell parameters (erythrocytes, haemoglobin and haematocrit) and a reduction in heart weight in rats.

These effects have also been observed for other AT1 receptor antagonists and for ACE-inhibitors and they seem to have been induced by the pharmacological action of high doses of olmesartan medoxomil and seem to be not relevant to humans at the recommended therapeutic doses.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Low substituted Hydroxypropylcellulose
Hydroxypropyl cellulose
Magnesium stearate

Tablet coating:
Polyethylene glycol
Hydroxypropylmethylcellulose
Titanium dioxide (E 171)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Olmesartan Hydrochlorothiazide Rowex is packed in following pack sizes:
Al//Al blister: 10, 14, 28, 30, 56, 60, 90 and 98 film-coated tablet
PVC/PVDC//Al blister: 10, 14, 28, 30, 56, 60, 90 and 98 film-coated tablet

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/240/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th August 2015

10 DATE OF REVISION OF THE TEXT

June 2021