AUSTRALIAN PRODUCT INFORMATION

OLMETEC PLUS®

(olmesartan medoxomil/hydrochlorothiazide) Tablets

1 NAME OF THE MEDICINE

Olmesartan medoxomil and hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OLMETEC PLUS consists of olmesartan medoxomil and hydrochlorothiazide (HCTZ).

OLMETEC PLUS 20/12.5 mg contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.

OLMETEC PLUS 20/25 mg contains 20 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide.

OLMETEC PLUS 40/12.5 mg contains 40 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.

OLMETEC PLUS 40/25 mg contains 40 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide.

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder. It is practically insoluble in water and sparingly soluble in methanol.

HCTZ is a white, or almost white, crystalline powder. HCTZ is very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

Excipients with known effect:

- lactose (as monohydrate)

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

OLMETEC PLUS is available for oral use as film-coated tablets containing 20/12.5 mg, 20/25 mg, 40/12.5 mg, or 40/25 mg olmesartan medoxomil/HCTZ.

OLMETEC PLUS (olmesartan medoxomil/hydrochlorothiazide) **20/12.5 mg** is a round tablet, approximately 8.5 mm in diameter, reddish yellow in colour with C22 debossed on one side.

OLMETEC PLUS (olmesartan medoxomil/hydrochlorothiazide) **20/25 mg** is a round tablet, approximately 8.5 mm in diameter, pinkish in colour with C24 debossed on one side. Not currently available in Australia.

OLMETEC PLUS (olmesartan medoxomil/hydrochlorothiazide) **40/12.5 mg** is an oval tablet, approximately 15 mm x 7 mm, reddish yellow in colour with C23 debossed on one side.

OLMETEC PLUS (olmesartan medoxomil/hydrochlorothiazide) **40/25 mg** is an oval tablet, approximately 15 mm x 7 mm in diameter, pinkish in colour with C25 debossed on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension.

Treatment should not be initiated with this fixed dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults
OLMETEC PLUS is administered once daily, with or without food, in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or HCTZ alone.

OLMETEC PLUS is registered in combinations of 20/12.5 mg, 20/25 mg, 40/12.5 mg and 40/25 mg (See **Section 6.5 Nature and Contents of Container** for marketed strengths).

Dosing should be individualised and dependent on the patient's condition. Depending on the blood pressure response, the dose may be titrated after 4 weeks.

If blood pressure is not adequately controlled on OLMETEC alone, HCTZ may be added with a starting dose of 12.5 mg. Should blood pressure still remain inadequately controlled either up-titration of HCTZ to 25 mg or OLMETEC to 40 mg dose may be advisable.

If blood pressure is not adequately controlled on HCTZ alone, olmesartan may be added with a starting dose of 20 mg with up-titration to 40 mg should blood pressure still remain inadequately controlled.

Doses of OLMETEC PLUS above 40/25 mg are not recommended.

Special populations

Elderly
No dosage adjustment is necessary.

If up-titration to the maximum dose of 40mg daily is required, blood pressure should be closely monitored.

Renal insufficiency
No adjustment of dosage is necessary for patients with mild (creatinine clearance of 50 –80 mL/min) to moderate (creatinine clearance of 30–<50 mL/min) renal impairment. When OLMETEC PLUS is used in such patients, periodic monitoring of renal function is advised (see **Section 4.4 Special Warnings and Precautions for Use**). OLMETEC PLUS is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) (see **Section 4.3 Contraindications**).

Intravascular volume depletion
For patients with possible depletion of intravascular volume, particularly those with impaired renal function, OLMETEC PLUS should be administered under close medical supervision.

If a patient becomes volume depleted whilst taking OLMETEC PLUS, blood pressure and renal function should be closely monitored until the situation resolves.

Hepatic insufficiency
No adjustment of dosage is necessary for patients with mild (Child-Pugh score 5 - 6) to moderate (Child-Pugh score 7 - 9) hepatic impairment. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe (Child-Pugh score 10 - 15) hepatic impairment (see **Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment**).

OLMETEC PLUS should not be used in patients with severe hepatic impairment, cholestasis and biliary obstruction (see **Section 4.3 Contraindications**).

If up-titration of the olmesartan medoxomil component to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored.

Children and adolescents
The safety and efficiency of OLMETEC PLUS in children have not been established.

4.3 CONTRAINDICATIONS

OLMETEC PLUS is contraindicated in:

- Patients who are hypersensitive to olmesartan medoxomil, sulfonamide derived drugs (e.g. thiazides), or any other component of this medication
- Pregnancy (see **Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy**)
- Patients with anuria or severe renal impairment (creatinine clearance <30 mL/min) (see **Section 4.4 Special Warnings and Precautions for Use, Use in renal impairment**)
- Patients with severe hepatic impairment (Child-Pugh score 10 - 15), cholestasis or biliary obstruction (see **Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment**)
- Patients who are breastfeeding
- Patients with refractory hypokalaemia, hypercalcaemia, hyponatraemia, and symptomatic hyperuricaemia (see **Section 4.4 Special Warnings and Precautions for Use, Electrolyte imbalance**)
- Patients with diabetes who are taking aliskiren (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravascular volume depletion

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

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 ACE inhibitors and angiotensin receptor antagonists has been associated with acute hypotension, azotaemia, oliguria or, rarely with acute renal failure and/or death. The possibility of similar effects cannot be excluded with olmesartan medoxomil.

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.

Hyperkalaemia

As with other angiotensin receptor antagonists and ACE inhibitors, hyperkalaemia may occur during treatment with OLMETEC PLUS, especially in the presence of renal impairment and/or heart failure. This is because OLMETEC PLUS contains olmesartan medoxomil, a drug which inhibits the renin-angiotensin system (RAS) and drugs that inhibit the RAS can cause hyperkalaemia. Concomitant use of OLMETEC PLUS with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products which may increase the potassium level (e.g. trimethoprim containing medicines) may lead to an increase in serum potassium. Close monitoring of serum potassium levels in at risk patients is recommended.

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.

Sprue-like enteropathy

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

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 drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of OLMETEC PLUS is not recommended in such patients.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been 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 HCTZ, 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, seizures, confusion, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see **Section 4.8 Adverse Effects (Undesirable Effects)**).

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with olmesartan medoxomil may reduce diuretic-induced hypokalaemia. 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. Conversely, due to antagonism at the angiotensin-II receptors (AT_1) through the olmesartan medoxomil component of OLMETEC PLUS hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. This is because olmesartan medoxomil inhibits the renin-angiotensin system (RAS) and drugs that inhibit the RAS can cause hyperkalaemia. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with OLMETEC PLUS (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

There is no evidence that olmesartan medoxomil would reduce or prevent diuretic-induced hyponatraemia.

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. Marked 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; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatraemia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Metabolic acidosis may occur. Although a chloride deficit in a particular patient is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with olmesartan medoxomil; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. OLMETEC PLUS should be immediately discontinued in patients who develop angioedema, and OLMETEC PLUS should not be re-administered.

Acute Respiratory Toxicity

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

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with OLMETEC PLUS, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Ethnic differences

As with all other angiotensin receptor antagonists, the blood pressure lowering effect of olmesartan medoxomil can be 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.

Lithium

The co-administration of OLMETEC PLUS and lithium is not recommended (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

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

Concomitant use of ACE inhibitors or angiotensin receptor antagonists and anti-inflammatory drugs and thiazide diuretics

The use of ACE-inhibitors or angiotensin receptor antagonists, and an anti-inflammatory drug (NSAID or COX-2 inhibitor), and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use with fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Other

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

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to HCTZ 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.

Use in hepatic impairment

OLMETEC PLUS should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma. Use of olmesartan medoxomil in patients with severe hepatic impairment (Child-Pugh score 10 - 15), cholestasis and biliary obstruction is contraindicated (see **Section 4.3 Contraindications**).

The pharmacokinetics of OLMETEC PLUS or coadministered olmesartan medoxomil and HCTZ have not been studied in patients with hepatic impairment.

Use in renal impairment

OLMETEC PLUS should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) (see **Section 4.2 Dose and Method of Administration**). No dosage adjustment is necessary in patients with mild (creatinine clearance 50 – 80 mL/min)to moderate (creatinine clearance 30 – <50 mL/min) renal impairment. In such patients OLMETEC PLUS should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. There is no experience of the administration of OLMETEC PLUS in patients with recent kidney transplantation.

The pharmacokinetics of OLMETEC PLUS or coadministered olmesartan medoxomil and HCTZ have not been studied in patients with renal impairment.

Use in the elderly

Clinical Studies of OLMETEC PLUS of 415 subjects aged 65 and over determined that the elderly do not respond differently from younger subjects. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Paediatric use

The safety and effectiveness of OLMETEC PLUS in children have not been established.

Effects on laboratory tests

Olmesartan medoxomil
In post-marketing experience, increased blood creatinine levels and hyperkalaemia have been reported.

HCTZ
Laboratory adverse events reports with HCTZ include the following: Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on OLMETEC PLUS

Medicinal products affecting potassium levels
The potassium-depleting effect of HCTZ 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, benzyl penicillin sodium or salicylic acid derivatives).

Conversely, 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, trimethoprim containing medicines) may lead to increases in serum potassium (see **Section 4.4 Special Warnings and Precautions for Use**).

If drugs which affect potassium levels are to be prescribed in combination with OLMETEC PLUS, monitoring of potassium plasma levels is advised.

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

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs (including acetylsalicylic acid at doses >3 g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment 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.

In some patients the administration of NSAIDs reduces the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when OLMETEC PLUS tablets and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Dual Blockade of the Renin-Angiotensin System (RAS)
Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on OLMETEC PLUS and other agents that affect the RAS.

Do not co-administer aliskiren with OLMETEC PLUS in patients with diabetes (see **Section 4.3 Contraindications**). Avoid use of aliskiren with OLMETEC PLUS in patients with renal impairment (GFR <60 ml/min).

Colesevelam hydrochloride
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. Consider administering olmesartan medoxomil 4 hours before the colesevelam hydrochloride dose.

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

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

Baclofen, amifostine
Potentiation of antihypertensive effect may occur.

Cholestyramine and colestipol resins
Absorption of HCTZ is impaired in the presence of anionic exchange resins.

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

Effects of OLMETEC PLUS on other medicinal products

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors and angiotensin II antagonists. Therefore, use of olmesartan and lithium in combination is not recommended (see **Section 4.4 Special Warnings and Precautions for Use, Lithium**). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when OLMETEC PLUS is administered with drugs affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes:

- 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).

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

Antidiabetic drugs (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required.

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

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.

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

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medications may be necessary since HCTZ 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.

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.

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 drugs and potentiate their myelosuppressive effects.

Additional information
Concomitant administration of olmesartan medoxomil and HCTZ had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

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 drugs metabolised by the above cytochrome P450 enzymes are expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of olmesartan and HCTZ in combination on fertility have not been investigated.

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1,000 mg/kg/day (relative plasma exposure of 7-8 times that anticipated at the MRHD based on AUC) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

No animal fertility studies are available for HCTZ.

Use in pregnancy

(Category D)

Olmesartan medoxomil
Drugs that act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking ACE inhibitors. When pregnancy is detected, OLMETEC PLUS should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and foetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. If pregnancy occurs during therapy, OLMETEC PLUS must be discontinued as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their foetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, OLMETEC PLUS should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of OLMETEC in pregnant women. No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1,000 mg/kg/day (7 times clinical exposure to olmesartan at MRHD based on AUC) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 basis; higher doses could not be evaluated for effects on foetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses $\geq$1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricula, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses $\geq$8 mg/kg/day. The no observed adverse effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

Thiazide diuretics
Thiazides cross the placental barrier and appear in cord blood. They may cause foetal electrolyte disturbances and possible other reactions that have occurred in adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy.

Use in lactation

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Thiazides appear in human milk.

Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of OLMETEC PLUS on the ability to drive and use machines has not been specifically studied. However, it should be borne in mind that dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Olmesartan medoxomil and HCTZ
The safety profile of olmesartan medoxomil/HCTZ has been evaluated in 2,341 hypertensive patients. This experience included 941 patients treated for at least 6 months, and 642 patients treated for at least 1-year.

Treatment with OLMETEC PLUS was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil/HCTZ.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil/HCTZ and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% of patients treated with olmesartan medoxomil/HCTZ and 2.0% of patients treated with placebo. The only adverse event which was statistically significantly more frequent on olmesartan medoxomil/HCTZ than on placebo was dizziness (2.9% versus 1.3%). The incidence of dizziness was not dose related.

Incidence of adverse events reported in all clinical trials with a greater than or equal to 1% incidence is shown in Table 1:

Table 1
Clinical adverse effects (all causalities) occurring in ≥1% of patients

Body system Adverse event	Number (%) patients with adverse event			
	OLMETEC PLUS (n=2,341)	Olmesartan medoxomil (n=2,847)	HCTZ (n=444)	Placebo (n=466)
Ear and labyrinth disorders				
Vertigo	30 (1.3)	30 (1.1)	5 (1.1)	4 (0.9)
Gastrointestinal disorders				
Diarrhoea	30 (1.3)	53 (1.9)	4 (0.9)	4 (0.9)
Dyspepsia	17 (0.7)	36 (1.3)	4 (0.9)	6 (1.3)
Nausea	22 (0.9)	39 (1.4)	1 (0.2)	4 (0.9)
General disorders and administration site conditions				
Chest pain	15 (0.6)	30 (1.1)	4 (0.9)	4 (0.9)
Fatigue	31 (1.3)	38 (1.3)	1 (0.2)	5 (1.1)
Influenza like illness	50 (2.1)	60 (2.1)	6 (1.4)	9 (1.9)
Oedema peripheral	12 (0.5)	34 (1.2)	2 (0.5)	6 (1.3)

Body system Adverse event	Number (%) patients with adverse event			
	OLMETEC PLUS (n=2,341)	Olmesartan medoxomil (n=2,847)	HCTZ (n=444)	Placebo (n=466)
Infections and infestations				
Bronchitis	98 (4.2)	100 (3.5)	21 (4.7)	20 (4.3)
Gastroenteritis	20 (0.9)	37 (1.3)	2 (0.5)	3 (0.6)
Influenza	23 (1.0)	36 (1.3)	3 (0.7)	6 (1.3)
Nasopharyngitis	49 (2.1)	70 (2.5)	10 (2.3)	13 (2.8)
Sinusitis	34 (1.5)	40 (1.4)	4 (0.9)	15 (3.2)
Upper respiratory tract infection	43 (1.8)	80 (2.8)	2 (0.5)	14 (3.0)
Urinary tract infection	41 (1.8)	42 (1.5)	6 (1.4)	3 (0.6)
Viral infection	4 (0.9)	12 (0.4)	1 (0.2)	5 (1.1)
Investigations				
ALT increased	19 (0.8)	36 (1.3)	3 (0.7)	4 (0.9)
AST increased	17 (0.7)	31 (1.1)	2 (0.5)	4 (0.9)
Blood creatinine increased	15 (0.6)	26 (0.9)	4 (0.9)	5 (1.1)
Blood glucose increased	21 (0.9)	18 (0.6)	5 (1.1)	12 (2.6)
Blood potassium decreased	8 (0.3)	2 (0.1)	5 (1.1)	0 (0.0)
Blood uric acid increased	31 (1.3)	11 (0.4)	4 (0.9)	6 (1.3)
Gamma GT increased	20 (0.9)	48 (1.7)	3 (0.7)	8 (1.7)
Musculoskeletal and connective tissue disorders				
Arthralgia	32 (1.4)	56 (2.0)	6 (1.4)	7 (1.5)
Back pain	72 (3.1)	102 (3.6)	10 (2.3)	8 (1.7)
Pain in limb	11 (0.5)	33 (1.2)	5 (1.1)	7 (1.5)
Spinal disorder	11 (0.5)	14 (0.5)	4 (0.9)	7 (1.5)
Nervous system disorders				
Dizziness	69 (2.9)	79 (2.7)	10 (2.3)	6 (1.3)
Headache	80 (3.4)	141 (5.0)	16 (3.6)	30 (6.4)
Psychiatric disorders				
Anxiety	4 (0.2)	11 (0.4)	2 (0.5)	5 (1.1)
Insomnia	16 (0.7)	30 (1.1)	1 (0.2)	9 (1.9)
Respiratory, thoracic and mediastinal disorders				
Cough	31 (1.3)	42 (1.5)	1 (0.2)	5 (1.1)
Pharyngitis	34 (1.5)	43 (1.5)	7 (1.6)	4 (0.9)

Adverse events reported across all clinical trials with olmesartan medoxomil/HCTZ (including trials with active as well as placebo control, irrespective of causality or incidence relative to placebo) include the events listed below. Frequencies are defined as: common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Cardiac disorders: Uncommon: Palpitations

Nervous system disorders: Uncommon: Syncope

General disorders:	Uncommon: Weakness
Investigations:	Uncommon: Blood potassium decreased, blood potassium increased, blood urea increased, increase SGOT, increase SGPT
Metabolism and nutrition disorders:	Common: Creatinine phosphokinase increased; Uncommon: Hyperuricaemia, hypertriglyceridaemia
Musculoskeletal and connective tissue disorders:	Uncommon: Arthritis
Skin and subcutaneous tissue disorders:	Uncommon: Rash, eczema
Renal and urinary disorders:	Uncommon: Haematuria
Vascular disorders:	Uncommon: Hypotension, orthostatic hypotension

Laboratory parameters
In clinical trials, clinically important changes in standard laboratory parameters were rarely associated with olmesartan medoxomil/HCTZ.

Creatinine, blood urea nitrogen: Increases in blood urea nitrogen (BUN) and serum creatinine of >50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil/HCTZ due to increased BUN or creatinine.

Haemoglobin and haematocrit: A greater than 20% decrease in haemoglobin and haematocrit was observed in 0.0% and 0.4% (n=1 patient), respectively, of olmesartan medoxomil/HCTZ patients, compared with 0.0% and 0.0%, respectively, in placebo-treated patients. No patients were discontinued due to anaemia.

Use in elderly
OLMETEC PLUS has been evaluated for safety in 415 patients aged 65 years or older of whom, 105 were aged 75 years or older. Overall the incidence of adverse events in the elderly is comparable to that of the adult population. The number of withdrawals due to olmesartan medoxomil/HCTZ-related adverse effects was low (8/415; 1.9%).

Adverse events reported with olmesartan medoxomil /HCTZ combination therapy in the elderly with a greater than 1% incidence are shown in table 2:

Table 2
Clinical adverse effects (all causalities) occurring in ≥1% of elderly patients

	Number (%) patients with adverse event			
Body System Adverse event	20 mg OM + HCTZ (n = 99)	40 mg OM + HCTZ (n = 316)	20 mg OM (n = 742)	40 mg OM (n = 464)
Gastrointestinal disorders				
Diarrhoea	0	4 (1.3%)	7 (0.9%)	5 (1.1%)
Infections and infestations				
Bronchitis	5 (5.1%)	6 (1.9%)	3 (0.4%)	7 (1.5%)
Bronchitis acute	2 (2.0%)	2 (0.6%)	8 (1.1%)	2 (0.4%)
Influenza	0	1 (0.3%)	9 (1.2%)	2 (0.4%)
Nasopharyngitis	2 (2.0%)	5 (1.6%)	16 (2.2%)	2 (0.4%)
Rhinitis	0	0	9 (1.2%)	2 (0.4%)
Urinary tract infection	0	3 (0.9%)	10 (1.3%)	7 (1.5%)

	Number (%) patients with adverse event			
Body System Adverse event	20 mg OM + HCTZ (n = 99)	40 mg OM + HCTZ (n = 316)	20 mg OM (n = 742)	40 mg OM (n = 464)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (1.0%)	2 (0.6%)	10 (1.3%)	4 (0.9%)
Back pain	4 (4.0%)	3 (0.9%)	8 (1.1%)	1 (0.2%)
Nervous system disorders				
Dizziness	0	9 (2.8%)	9 (1.2%)	8 (1.7%)
Headache	3 (3.0%)	3 (0.9%)	13 (1.8%)	13 (2.8%)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (1.0%)	3 (0.9%)	8 (1.1%)	6 (1.3%)

The most common adverse events considered to be treatment related in elderly patients on 20 mg olmesartan medoxomil with HCTZ were headache (2.0%) and cough (1.0%). The most common adverse event considered to be treatment related in elderly patients on 40 mg olmesartan medoxomil with HCTZ was dizziness (1.3%).

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:

General disorders and administration site conditions:	Asthenic conditions, such as asthenia, fatigue, lethargy, malaise
Gastrointestinal disorders:	Abdominal pain; nausea; vomiting
Investigations:	Hepatic enzymes increased; blood calcium increased; blood lipids increased; increased blood creatinine levels
Metabolism and nutrition disorders:	Hyperkalaemia; hypercholesterolaemia
Musculoskeletal and connective tissue disorders:	Rhabdomyolysis; myalgia; muscle spasm
Nervous system disorders:	Headache; disturbances in consciousness; postural dizziness; somnolence
Reproductive system and breast disorders:	Erectile dysfunction
Respiratory, thoracic and mediastinal disorders:	Cough
Skin and subcutaneous tissue disorders:	Angioedema; alopecia; rash; pruritus; urticaria
Renal and urinary disorders:	Acute renal failure
Vascular disorders:	Flushing

Additional information on individual components

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

Olmesartan medoxomil
In double-blind, placebo-controlled monotherapy studies, the overall incidence of treatment-emergent adverse events was similar on olmesartan medoxomil and on placebo. In long-term (2-year) treatment, the incidence of withdrawals due to adverse events on olmesartan medoxomil 20 mg once daily was 3%.

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 following adverse events have been reported across all clinical trials with olmesartan medoxomil irrespective of causality or incidence relative to placebo. They are listed under body system and ranked under headings of frequency using the conventions described above:

Cardiovascular:	Uncommon: Tachycardia; Rare: Hypotension
Central nervous system:	Common: Dizziness; Uncommon: Vertigo
Gastro-intestinal:	Common: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea
General:	Common: Chest pain, fatigue, headache, influenza-like symptoms, peripheral oedema, pain
Musculoskeletal:	Common: Arthritis, back pain, skeletal pain; Uncommon: Arthralgia, myalgia
Myo/endo/pericardial and valve disorders:	Uncommon: Angina pectoris
Respiratory system:	Common: Bronchitis, cough, pharyngitis, rhinitis, sinusitis
Skin and appendages:	Uncommon: Rash
Urinary system:	Common: Haematuria, urinary tract infection

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

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

Metabolic and nutritional:	Common: Increased creatine phosphokinase, hyperglycaemia, hypertriglyceridaemia, hyperuricaemia, blood urea increased; Uncommon: Hypercholesterolaemia, hyperlipaemia; Rare: Hyperkalaemia
Liver and biliary:	Common: Liver enzyme elevations
Investigations:	Decrease in haemoglobin and haematocrit

Post-marketing experience
The following adverse reactions have been reported in post-marketing experience:

Blood and lymphatic system disorders:	Thrombocytopenia
General disorders and administration site conditions:	Peripheral oedema; asthenic conditions, such as asthenia, fatigue, lethargy, malaise
Gastrointestinal disorders:	Abdominal pain; nausea; vomiting; diarrhoea; sprue-like enteropathy
Hepatobiliary disorders:	Autoimmune hepatitis
Immune system disorders:	Anaphylactic reactions
Investigations:	Hepatic enzymes increased; increased blood creatinine levels; blood urea increased
Metabolism and nutrition disorders:	Hyperkalaemia
Musculoskeletal and connective tissue disorders:	Rhabdomyolysis; myalgia; muscle spasm
Nervous system disorders:	Headache
Respiratory, thoracic and mediastinal disorders:	Cough
Skin and subcutaneous tissue disorders:	Angioedema; alopecia; rash; pruritus; urticaria; allergic dermatitis; exanthema
Renal and urinary disorders:	Acute renal failure
Vascular disorders:	Flushing

ROADMAP/ORIENT

Two post marketing studies were conducted to determine the effects of olmesartan on renal disease in diabetic patients. In both of these studies, cardiovascular events were exploratory secondary efficacy endpoints. Cardiovascular deaths occurred in higher proportions of patients treated with olmesartan than placebo, but the risk of non-fatal myocardial infarction was lower with olmesartan.

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could prevent or delay the onset of microalbuminuria. This is not an approved indication in Australia. During the median follow-up duration of 3.2 years, patients received either olmesartan 40 mg or placebo once daily in addition to other antihypertensive agents, except ACE inhibitors or angiotensin receptor blockers (ARBs).

In this study, cardiovascular events were exploratory secondary efficacy endpoints. The endpoints were classed as cardiovascular (CV) morbidity endpoints and CV mortality endpoints. The CV morbidity endpoints included acute coronary syndrome (ACS), congestive heart failure (CHF), silent myocardial infarction (MI), coronary revascularisation (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft [CABG]), stroke, peripheral vascular disease (PVD), new-onset atrial fibrillation (AF), and transient ischaemic attack (TIA). The CV Mortality endpoints includes: sudden cardiac death, fatal MI, fatal stroke,

CHF death, death post PTCA or CABG, recent MI on autopsy. The study was not designed to formally compare the treatment groups in relation to these endpoints.

Cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. There was a finding of increased cardiovascular mortality in the olmesartan group, compared with the placebo group (15 patients (0.7%) vs 3 patients (0.1%)) (HR 4.9, 95%CI (1.4, 17.1), exploratory p value =0.0115). Conversely, a smaller proportion of patients had a non-fatal myocardial infarction in the olmesartan group compared with the placebo group (17 patients (0.8%) vs 26 patients (1.2%)), (HR 0.64, 95% CI (0.35, 1.18)) and the same proportions of patients in each treatment group were reported with non-cardiovascular mortality (11 patients (0.5%) vs 12 patients (0.5%)). Non-fatal stroke was reported in 14 patients (0.6%) in the olmesartan group and 8 patients (0.4%)) in the placebo group. Overall mortality with olmesartan was numerically increased compared with placebo (26 patients (1.2%) vs 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events (sudden cardiac death (7 (0.3%) vs 1 (0.0%)) and fatal myocardial infarction (5 (0.2%) vs 0 (0.0%)).

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) primarily investigated the suppressive effect of olmesartan on the progression of diabetic nephropathy in 577 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. This is not an approved indication in Australia. 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 once daily dose of olmesartan was up-titrated from 10 mg to 20 mg to 40 mg, subject to tolerability and safety. Not all patients received the 40 mg dose. The study (undertaken in Japan and in Hong Kong) was not designed to formally compare the treatment groups in relation to cardiovascular endpoints. The composite cerebro/cardiovascular endpoint, an exploratory secondary efficacy endpoint, occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite endpoint included cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction as well as additional individual endpoints. Cardiovascular death was reported in 10 patients (3.5%) receiving olmesartan compared with 3 patients (1.1%) receiving placebo. Sudden death occurred in 5 patients (1.8%) in the olmesartan group compared with 2 patients (0.7%) in the placebo group. Overall mortality, non-fatal stroke and non-fatal myocardial infarction were reported, however, in lower proportions of patients treated with olmesartan compared with placebo (overall mortality 19 patients (6.7%) vs 20 patients (7.0%), non-fatal stroke 8 patients (2.8%) vs 11 patients (3.9%) and non-fatal myocardial infarction 3 patients (1.1%) vs 7 patients (2.5%) (olmesartan vs placebo, respectively)).

Use in elderly patients

OLMETEC has been evaluated for safety in 1646 patients aged 65 years or older of whom, 454 were aged 75 years or older. Overall the incidence of adverse events in the elderly is comparable to that of the adult population. The number of withdrawals due to olmesartan medoxomil-related adverse effects was very low (6/1206; 0.5%) compared to the placebo (1/85; 1.2%) or losartan (0/184; 0.0%)

The most common adverse events considered to be treatment related in elderly patients were headache (1.5%) and dizziness (1.1%) on 40mg olmesartan medoxomil.

HCTZ

HCTZ may cause or exacerbate volume depletion, which may lead to electrolyte imbalance (see **Section 4.4 Special Warnings and Precautions for Use**).

Adverse events reported with the use of HCTZ alone include:

Blood and lymphatic system disorders:	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression
Cardiac disorders:	Cardiac arrhythmias
Ear and labyrinth disorders:	Vertigo
Eye disorders:	Xanthopsia, transient blurred vision, diplopia, lacrimation decreased, worsening of pre-existing myopia, acute angle-closure glaucoma, choroidal effusion (frequency not known). Cases of choroidal effusion with visual field defect have been reported after the use of thiazide diuretics.
Gastrointestinal disorders:	Gastric irritation, diarrhoea, constipation, pancreatitis, abdominal pain, meteorism, paralytic ileus, vomiting, nausea, cramping
General disorders and administration site conditions:	Fever
Hepatobiliary disorders:	Jaundice (intrahepatic cholestatic jaundice), acute cholecystitis
Immune system disorders:	Anaphylactic reactions
Infections and infestations:	Sialadenitis
Investigations:	Blood creatinine increased; blood urea increased
Metabolism and nutritional disorders:	Loss of appetite, Hypercholesterolaemia, hyperuricaemia, hypertriglyceridaemia, glycosuria, hypercalcaemia, hyperglycaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, hyperamylasaemia, hypochloraemic alkalosis, hypochloraemia
Musculoskeletal and connective tissue disorders:	Muscle spasm, muscular weakness
Nervous system disorders:	Headache, paresis, light-headedness, paraesthesia, convulsions, dizziness
Psychiatric disorders:	Anorexia, restlessness, sleep disturbances, depression, confusional state, apathy
Reproductive system and breast disorders:	Erectile dysfunction
Respiratory, thoracic and mediastinal disorders:	Respiratory distress, pneumonitis, pulmonary oedema, dyspnoea and interstitial pneumonia. Acute respiratory distress has been reported in very rare instances (see Section 4.4 Special Warnings and Precautions for Use).

Skin and subcutaneous tissue disorders:	Photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus, erythematosus, urticaria, erythema multiforme, exfoliative dermatitis including Stevens-Johnson syndrome and toxic epidermal necrolysis, erythema, pruritus, purpura
Renal and urinary disorders:	Renal failure, renal dysfunction, interstitial nephritis
Vascular disorders:	Postural hypotension, embolism, thrombosis, necrotising angiitis (vasculitis, cutaneous vasculitis)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No specific information is available on the effects or treatment of OLMETEC PLUS overdosage. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

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

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OLMETEC PLUS is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, HCTZ. 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 OLMETEC PLUS provides an effective and smooth reduction in blood pressure over the 24-hour dose interval.

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan medoxomil is an orally active angiotensin II receptor (type AT_1) antagonist. It has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor. 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 plays a significant role in the pathophysiology of hypertension via the type 1 (AT_1) receptor.

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

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

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

HCTZ 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 HCTZ 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 co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With HCTZ, 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.

The combination of olmesartan medoxomil and HCTZ produces additive reductions in blood pressure, which generally increase with the dose of each component. In pooled placebo-controlled studies, administration of the 20/12.5 mg, 20/25 mg, 40/12.5 mg, and 40/25 mg combinations of olmesartan medoxomil/HCTZ resulted in mean placebo-subtracted systolic/diastolic blood pressure reductions at trough ranging from 12/7 to 16/9 mmHg. Age and gender had no clinically relevant effect on response to treatment with olmesartan medoxomil/HCTZ combination therapy.

Administration of 12.5 mg and 25 mg HCTZ 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 mmHg and 12/7 mmHg, respectively, compared with olmesartan medoxomil monotherapy baseline. The additional mean systolic/diastolic blood pressure reductions at trough compared with baseline, measured conventionally, were 11/10 mmHg and 16/11 mmHg, respectively. The addition of 12.5 mg HCTZ in patients not achieving target blood pressure ($\leq$130/85 mmHg) on olmesartan medoxomil 40 mg decreased systolic/diastolic blood pressure by an additional 13/6 mmHg,

and titration of the HCTZ dose to 25 mg in non-achievers at the lower add-on dose resulted in a further blood pressure decrease of 9/5 mmHg. Conversely, addition of olmesartan medoxomil 10–20 mg in patients with moderate to severe hypertension insufficiently controlled by HCTZ 25 mg monotherapy provided mean systolic/diastolic blood pressure reductions at trough of 21/18 mmHg compared with HCTZ monotherapy baseline.

The effectiveness of olmesartan medoxomil/HCTZ combination therapy was maintained over long-term (1-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant HCTZ therapy, did not result in rebound hypertension.

The effects of fixed dose combination of olmesartan medoxomil/HCTZ on mortality and cardiovascular morbidity are currently unknown.

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 71,553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 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).

Clinical trials

Olmesartan medoxomil

The antihypertensive effects of OLMETEC have been demonstrated in seven placebo-controlled studies at doses ranging from 2.5 to 80 mg for 6 to 12 weeks. Approximately 2,800 patients with essential hypertension were studied. The blood pressure lowering effect of OLMETEC tended to increase with time and to increase with dose up to the 40 mg dose. OLMETEC 10 mg (n=521), 20 mg (n=513), and 40 mg (n=195) once daily produced statistically significant reductions in peak and trough blood pressure compared with placebo (n=543) at every time point from Week 2 to Week 12 (sSBP $p<0.001$ and sDBP $p<0.001$). The blood pressure lowering effect was maintained throughout the 24-hour period with OLMETEC once daily, with trough-to-peak ratios for systolic and diastolic response between 60 and 80%.

The blood pressure lowering effect of OLMETEC, with and without HCTZ, was maintained in patients treated for up to 1-year. There was no evidence of tachyphylaxis during long-term treatment with OLMETEC or rebound effect following abrupt withdrawal of olmesartan medoxomil after 1-year of treatment.

The antihypertensive effect of OLMETEC was similar in men and women and in patients older and younger than 65 years. The effect was smaller in black patients (usually a low-renin population), as has been seen with other ACE inhibitors, angiotensin receptor blockers and beta-blockers. OLMETEC had an additional blood pressure lowering effect when added to HCTZ.

Olmesartan medoxomil and HCTZ

In clinical trials, 1,230 patients were exposed to the combination of olmesartan medoxomil (2.5 mg to 40 mg) and HCTZ (12.5 mg to 25 mg). These trials included one placebo-controlled factorial trial (n=502) in mild-moderate hypertensives with combinations of olmesartan medoxomil (10 mg, 20 mg, 40 mg or placebo) and HCTZ (12.5 mg, 25 mg or placebo). The

antihypertensive effect of the combination on trough blood pressure was related to the dose of each component (see Table 3 below).

Table 3
Placebo-adjusted changes in sitting systolic and diastolic blood pressure (mmHg)

HCTZ dose	Olmesartan medoxomil dose			
	Placebo	10 mg	20 mg	40 mg
Placebo	—	7/5	12/5	13/7
12.5 mg	5/1	17/8	17/8	16/10
25 mg	14/5	19/11	22/11	24/14

Once daily dosing with 20 mg olmesartan medoxomil and 12.5 mg HCTZ, 40 mg olmesartan medoxomil and 12.5 mg HCTZ or 40 mg olmesartan medoxomil and 25 mg HCTZ produce mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) ranging from 17/8 to 24/14 mmHg.

The onset of the antihypertensive effect occurred within 1-week and was near maximal at 4 weeks. The antihypertensive effect was independent of gender, but there were too few subjects to identify response differences based on race or age greater than or less than 65 years. No appreciable changes in trough heart rate were observed with combination therapy in the placebo-controlled trial.

Use in the elderly
The antihypertensive effects of OLMETEC PLUS were investigated in a randomised, double-blind, parallel group with losartan in elderly patients (65 years or older; olmesartan n=251 whom 69 were >75 years; losartan n=130 whom 48 were >75 years) with essential hypertension for 52 weeks. Patients were initiated on a starting dose of 20mg OLMETEC. At 4 week intervals, the treatment was titrated to achieve target BP. The results obtained for those on OLMETEC PLUS were similar to those in the losartan group.

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 (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.

The mean volume of distribution after intravenous dosing is in the range of 16–29 litres. Olmesartan is highly bound to plasma proteins (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound co-administered drugs is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan crossed the placental barrier in rats and was distributed to the foetus. Olmesartan was distributed to milk at low levels in rats.

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

Metabolism and excretion

Olmesartan medoxomil
Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan.

Total plasma clearance was typically 1.3 L/h (CV, 19%) and was relatively slow compared with hepatic blood flow (approximately 90 L/h). Approximately 30% to 50% of the systemically absorbed drug is excreted in the urine whilst the remainder is excreted in faeces (via the bile).

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.

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

Pharmacokinetics in special populations

Elderly
In hypertensive patients, the AUC at steady state was increased by approximately 33% in elderly patients (65–75 years old) and by approximately 31% (adjusted for gender and body mass index) in very elderly patients (≥75 years old) compared with the younger age group (See **Section 4.2 Dose and Method of Administration**).

Paediatric
The pharmacokinetics of olmesartan have not been investigated in patients <18 years of age.

Gender
Minor differences were observed in the pharmacokinetics of olmesartan in women compared with men. AUC and C_{max} were 10–15% higher in women than in men. Female patients had approximately 20% smaller clearances of hydrochlorothiazide than male patients.

Renal impairment
In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <30 mL/min)) (See **Section 4.2 Dose and Method of Administration** and **Section 4.4 Special Warnings and Precautions for Use**, **Use in renal impairment**).

The pharmacokinetics of olmesartan in patients undergoing haemodialysis has not been studied.

Hepatic impairment
Mean olmesartan AUC after single oral administration to patients with moderate hepatic impairment (Child-Pugh score 7 - 9) was increased by about 48% compared with healthy controls (total group), or by about 60% when compared with matched controls only. Following repeated dosing, a similar increase in olmesartan mean AUC was observed in patients with moderate hepatic impairment (Child-Pugh score 7 - 9) when compared with matched healthy controls. Olmesartan mean C_{max} values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (Child-Pugh score 10 - 15) (See **Section 4.2 Dose and Method of Administration** and **Section 4.4 Special Warnings and Precautions for Use**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Olmesartan medoxomil
Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the intestine and kidney of a mutagenic susceptible mouse (MutaMouse) and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2,000 mg/kg/day. Olmesartan not tested in this mouse model. On balance, the weight-of-evidence indicates that olmesartan medoxomil does not pose a genotoxic risk at clinically relevant doses.

HCTZ
HCTZ was negative in several different assays of gene mutation and chromosomal aberration. However, positive test results were obtained in the *in vitro* CHO sister chromatid exchange (clastogenicity) assay and the mouse lymphoma (mutagenicity) assay at HCTZ concentrations of 43–1,200 µg/mL.

Olmesartan medoxomil and HCTZ
Olmesartan medoxomil/HCTZ in a ratio of 20:12.5 was negative in the bacterial reverse mutation test up to the maximum recommended plate concentration for the standard assays. As expected, positive clastogenicity responses were observed with either drug or the combination (40:12.5, 20:12.5, 10:12.5) in Chinese hamster lung cells but no synergistic clastogenicity was observed. However, the combination (20:12.5) was negative in the *in vivo* mouse micronucleus test at oral doses (1,935/1,209 mg/kg) that were likely to achieve high relative systemic exposure (>33–700-fold based on AUC) to both components.

Carcinogenicity

The carcinogenic potential of olmesartan and HCTZ in combination has not been investigated.

Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2,000 mg/kg/day) corresponded to a relative systemic exposure to olmesartan that was about 30 times that anticipated at the maximum recommended human dose (MRHD) of 40 mg/day (based on AUC). Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1,000 mg/kg/day (about 11 times anticipated clinical exposure to olmesartan at the MRHD, based on AUC in Hras2), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential for HCTZ in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats

at doses up to approximately 100 mg/kg/day. There was equivocal evidence for hepatocarcinogenicity in male mice treated with HCTZ at approximately 600 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OLMETEC PLUS tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hyprolose, magnesium stearate, and Opadry O2A22352 or Opadry O2A24576. These contain titanium dioxide, purified talc, hypromellose, and iron oxides.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

OLMETEC PLUS is available in blister packs of 10 and 30 film-coated tablets.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

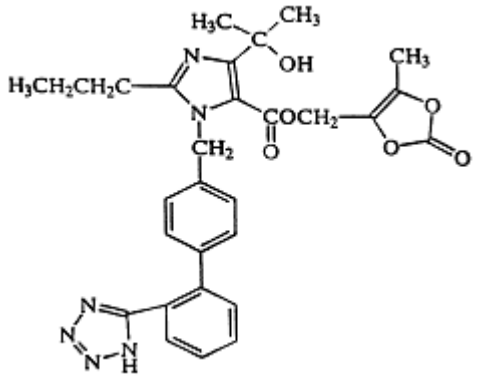
Olmesartan medoxomil is a prodrug, hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist. HCTZ is a thiazide diuretic.

Olmesartan medoxomil is described chemically as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-*[p-(o*-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is $C_{29}H_{30}N_6O_6$. It has a molecular weight of 558.59.

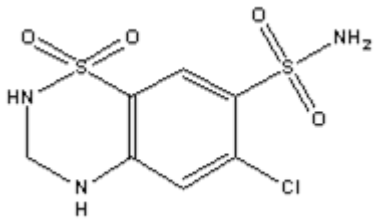
HCTZ is described chemically as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The empirical formula is $C_7H_8ClN_3O_4S_2$. It has a molecular weight of 297.7.

Chemical structure

The structural formula of olmesartan medoxomil is:



The structural formula of hydrochlorothiazide is:



CAS number

The CAS Registry Number of olmesartan medoxomil is 144689-63-4.

The CAS Registry Number of hydrochlorothiazide is 58-93-5.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

13 May 2011

10 DATE OF REVISION

23 August 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of acute respiratory toxicity with hydrochlorothiazide use
4.8	Addition of autoimmune hepatitis and acute respiratory distress as an adverse reaction in the post-marketing subsection.

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