AUSTRALIAN PRODUCT INFORMATION

OLSETAN

(olmesartan medoxomil)
Tablets

1 NAME OF THE MEDICINE

Olmesartan medoxomil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains either 10 mg, 20 mg or 40 mg of olmesartan medoxomil

List of excipients with known effect:

- lactose (as monohydrate)

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

3 PHARMACEUTICAL FORM

10 mg tablet: White to off-white, round, biconvex, film coated tablets, debossed with “IO2” on one side and plain on other side.

20 mg tablet: White to off-white, round, biconvex, film coated tablets, debossed with “IO3” on one side and plain on other side.

40 mg tablet: White to off-white, oval, biconvex, film coated tablets, debossed with “IO4” on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OLSETAN is indicated for the treatment of hypertension.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Dosage must be individualised. The optimal recommended starting dose of OLSETAN is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. If additional blood pressure reduction is required, the dose of OLSETAN may be increased to a maximum of 40 mg daily.

OLSETAN may be administered with or without food. In order to assist compliance, it is recommended that OLSETAN tablets be taken at about the same time each day. Twice-daily dosing offers no advantage over the same total dose given once daily.

The antihypertensive effect of olmesartan medoxomil is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose regimen for any patient. Hydrochlorothiazide therapy should be considered in those patients requiring additional blood pressure control beyond 40 mg daily. OLSETAN may be administered with other antihypertensive agents.

Special populations

Elderly
No dosage adjustment is necessary.

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

Renal insufficiency
No adjustment of dosage is required for patients with mild (creatinine clearance of 50-80 mL/min, eGFR 60-89 mL/min/1.73 m^2) to moderate (creatinine clearance of 30 - <50 mL/min, eGFR 30-59 mL/min/1.73 m^2) renal impairment. The use of OLSETAN in patients with severe renal impairment (creatinine clearance <30 mL/min, eGFR <30 mL/min/1.73 m^2) is not recommended, since there is only limited experience in this patient group (see **Section 4.4 Special Warnings and Precautions for Use, Use in renal impairment**). There are no data on the use of olmesartan in children with eGFR less than 25 mL/min/1.73 m^2.

Intravascular volume depletion
For patients with possible depletion of intravascular volume, particularly those with impaired renal function, OLSETAN should be administered under close medical supervision. In these patients a lower starting dose of 10 mg once daily is recommended (see **Section 4.4 Special Warnings and Precautions for Use, Intravascular volume depletion**) (see **Section 6.5 Nature and Contents of Container** for marketed strengths).

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

Hepatic insufficiency
No adjustment of dosage is required 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**).

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

Paediatric Use
Dosing must be individualised. The recommended starting dose of OLSETAN is based on age and/or weight (see dosing recommendation in Table 1). If after 2 weeks of therapy further reduction in blood pressure is required, the dose of OLSETAN may be increased to a maximum of either 20 mg or 40 mg (see Dosing recommendation in Table 1). There are limited data available for the pharmacokinetics of olmesartan in children aged less than 6 years (see **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Paediatric**) and there are no pharmacokinetic data available in children with renal impairment (see **Section 4.2 Dose and Method of Administration, Renal insufficiency**).

Table 1
Dosing recommendations

Age Group	Weight	Starting Dose Once daily	Dose Range Once daily	Maximum dose Once daily
1-5 years	≥ 5 kg	0.3 mg/kg Max: 10 mg	0.3 – 0.6 mg/kg Max: 20 mg	20 mg
6-18 years	≥ 20 kg and < 35 kg	10 mg	10 – 20 mg	20 mg
	≥ 35 kg	20 mg	20 – 40 mg	40 mg

For children who cannot swallow tablets, the equivalent dose may be given as an extemporaneous suspension [see **Section 4.2 Dose and Method of Administration, Special Populations, Preparation of suspension by compounding pharmacist (for 200 mL of a 2 mg/mL suspension)**].

If 10 mg tablets are not available, the extemporaneous suspension may be used.

Preparation of Suspension by compounding pharmacist (for 200 mL of a 2 mg/mL suspension)
The suspension is prepared in an amber polyethylene terephthalate (PET) bottle with a child resistant closure. The amber PET bottle should be of a suitable size e.g. 240 mL*

* The stability of the suspensions in larger bottles has not been established.

Add 50 mL of purified water to an amber PET bottle containing **twenty** OLSETAN **20 mg tablets** and allow it to stand for a minimum of 5 minutes to allow complete disintegration. Shake the container for at least 1 minute and allow the suspension to stand for at least 1 minute. Repeat 1-minute shaking and 1 minute standing steps for **four additional times**. Add 100 mL of Ora-Sweet®* and 50 mL of Ora-Plus®* to the suspension and shake well for at least 1-minute.

*Ora-Sweet® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

Ora-Sweet® contains citric acid, flavouring, glycerine, methylparaben, potassium sorbate, sodium phosphate, sorbitol, sucrose, and purified water. Ora-Plus® contains calcium sulphate, carrageenan, citric acid, dimethicone antifoam emulsion, methylparaben, microcrystalline cellulose, sodium carboxymethylcellulose, potassium sorbate, sodium phosphate monobasic, trisodium phosphate, xanthan gum, and purified water.

The suspension cannot be prepared using water only and the tablets should not be ground before use. Only 20 mg OLSETAN tablets may be used in preparing the suspension. For handling and storage instruction, see **Section 6.4 Special Precautions for Storage.**

4.3 CONTRAINDICATIONS

OLSETAN is contraindicated in:

Patients who are hypersensitive to either olmesartan medoxomil or any component of this medication.
Pregnancy (see **Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy**).
Patients with 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) or biliary obstruction (see **Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment**).
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 olmesartan medoxomil.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with 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 drugs that affect the renin-angiotensin-aldosterone system.

Hyperkalaemia

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

Lithium

As with other angiotensin receptor antagonists, the combination of lithium and OLSETAN is not recommended (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy

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

Primary aldosteronism

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

Ethnic differences

As with all other angiotensin receptor antagonists, the blood pressure lowering effect of OLSETAN 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.

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.

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 OLSETAN in cases where no other etiology is identified.

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. OLSETAN should be immediately discontinued in patients who develop angioedema, and OLSETAN should not be re-administered.

General

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

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.

Use in hepatic impairment

There is no experience in patients with severe hepatic impairment (Child-Pugh score 10 - 15) and therefore use of OLSETAN in this patient group is not recommended (see **Section 4.2 Dose and Method of Administration**).

Use in renal impairment

When olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of OLSETAN is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min, eGFR <30 mL/min/1.73 m^2) (see **Section 4.2 Dose and Method of Administration**). There is no experience of the administration of OLSETAN in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance <12 mL/min, eGFR <15 mL/min/1.73 m^2). There are no data on the use of olmesartan in children with eGFR less than 25 mL/min/1.73 m^2.

Use in the elderly

Of the total number of hypertensive patients receiving olmesartan medoxomil in clinical studies, including two studies investigating safety and efficacy in the elderly, more than 40% were 65 years of age and over, while more than 10% were 75 years of age and older. No overall differences in

effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric use

Not to be used for children aged below 1 year of age. Pharmacokinetic information is limited in patients less than 6 years.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that affect OLSETAN

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

Other antihypertensive medications
The blood pressure lowering effect of OLSETAN 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 receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin receptor 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 receptor antagonists, leading to their partial loss of efficacy.

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 OLSETAN and other agents that affect the RAS.

Do not co-administer aliskiren with OLSETAN in patients with diabetes (see **Section 4.3 Contraindications**). Avoid use of aliskiren with OLSETAN 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. Coadministration of warfarin and digoxin had no effect on the pharmacokinetics of olmesartan.

Drugs that are affected by OLSETAN

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors and angiotensin receptor antagonists. Therefore, use of OLSETAN 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.

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

Olmesartan had no clinically relevant inhibitory effects on *in vitro* human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal inducing effects on rat cytochrome P450 activities. Therefore *in vivo* interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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.

Use in pregnancy (Category D)

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, OLSETAN 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 receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of OLSETAN 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, OLSETAN 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 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 olmesartan medoxomil 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 ≥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 ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

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. 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 OLSETAN tablets on the ability to drive has not been specifically studied. With respect to driving vehicles or operating machines, it should be taken into account that occasionally dizziness or fatigue may occur in patients taking antihypertensive therapy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Olmesartan medoxomil has been evaluated for safety in more than 3,825 patients/subjects, including more than 3,275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year.

Treatment with olmesartan medoxomil 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.

The overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e. 79/3,278) of patients treated with olmesartan medoxomil and 2.7% (i.e. 32/1,179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence versus placebo was dizziness (2.5% versus 0.9%).

Adverse events reported in placebo-controlled monotherapy studies with a greater than 1% incidence are shown in Table 2.

Table 2

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

Body system Adverse event	Number (%) patients with adverse event			
	Placebo (n=555)	10 mg (n=528)	20 mg (n=566)	40 mg (n=195)
Body as a whole – general disorders				
Back pain	8 (1.4)	5 (1.0)	5 (0.9)	3 (1.5)
Chest pain	3 (0.5)	2 (0.4)	4 (0.7)	2 (1.0)
Fatigue	5 (0.9)	7 (1.3)	8 (1.4)	0 (0.0)
Headache	48 (8.7)	25 (4.7)	32 (5.7)	9 (4.6)
Influenza-like symptoms	18 (3.2)	17 (3.2)	17 (3.0)	7 (3.6)
Oedema peripheral	4 (0.7)	2 (0.4)	3 (0.5)	2 (1.0)
Pain	3 (0.5)	3 (0.6)	4 (0.7)	3 (1.5)
Central & peripheral nervous disorders				
Dizziness	5 (0.9)	8 (1.5)	14 (2.5)	6 (3.1)
Gastrointestinal system				
Diarrhoea	3 (0.5)	3 (0.6)	6 (1.1)	2 (1.0)
Dyspepsia	6 (1.0)	1 (0.2)	5 (0.8)	1 (0.5)
Gastroenteritis	0 (0.0)	3 (0.6)	9 (1.6)	0 (0.0)
Nausea	5 (0.9)	1 (0.2)	4 (0.7)	4 (2.1)
Tooth ache	2 (0.4)	1 (0.2)	3 (0.5)	3 (1.5)
Liver and biliary system disorders				
Bilirubinaemia	2 (0.36)	1 (0.2)	5 (0.9)	0 (0.0)
Gamma-GT increased	11 (2.0)	15 (2.8)	10 (1.8)	4 (2.1)
Increased SGOT	6 (1.1)	9 (1.7)	1 (0.2)	0 (0.0)
Increased SGPT	9 (1.6)	9 (1.7)	4 (0.7)	2 (1.0)
Metabolic and nutritional disorders				
Gout	1 (0.2)	2 (0.4)	2 (0.4)	2 (1.0)
Creatine phosphokinase increased	4 (0.7)	2 (0.4)	9 (1.6)	1 (0.5)
Hyperglycaemia	14 (2.5)	5 (1.0)	7 (1.2)	5 (2.6)
Hypertriglyceridaemia	6 (1.1)	11 (2.1)	12 (2.1)	4 (2.1)
Hyperuricaemia	5 (0.9)	5 (1.0)	10 (1.8)	0 (0.0)
Musculoskeletal system				
Arthralgia	4 (0.7)	3 (0.6)	6 (1.1)	0 (0.0)
Arthritis	1 (0.2)	3 (0.6)	0 (0.0)	2 (1.0)
Skeletal pain	3 (0.5)	5 (1.0)	6 (1.1)	1 (0.5)
Psychiatric disorders				
Anxiety	2 (0.4)	2 (0.4)	2 (0.4)	2 (1.0)
Insomnia	8 (1.4)	1 (0.2)	9 (1.6)	1 (0.5)
Reproductive disorders, male				
Impotence	0 (0.0)	2 (0.4)	2 (0.4)	4 (2.1)
Respiratory system				
Upper respiratory tract infection	26 (4.7)	14 (2.7)	10 (1.8)	7 (3.6)
Bronchitis	10 (1.8)	11 (2.1)	12 (2.1)	5 (2.6)
Coughing	4 (0.7)	3 (0.6)	6 (1.1)	2 (1.0)
Pharyngitis	6 (1.1)	9 (1.7)	5 (0.9)	1 (0.5)
Rhinitis	9 (1.6)	9 (1.7)	6 (1.1)	2 (1.0)
Sinusitis	12 (2.2)	6 (1.1)	8 (1.4)	2 (1.0)
Secondary terms				
Inflicted injury	3 (0.5)	7 (1.3)	4 (0.7)	1 (0.5)
Urinary system disorders				
Haematuria	10 (1.8)	8 (1.5)	15 (2.7)	4 (2.1)
Urinary tract infection	4 (0.7)	1 (0.2)	6 (1.1)	3 (1.5)

Other adverse events of potential clinical relevance reported in the clinical trials are listed below. Adverse events reported across all clinical trials with olmesartan medoxomil (including trials with active as well as placebo control), irrespective of causality or incidence relative to placebo, included those 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).

Cardiovascular: Uncommon: Tachycardia;
Rare: Hypotension
Central nervous system: Uncommon: Vertigo
Gastro-intestinal: Common: Abdominal pain
Myo/endo/pericardial and valve disorders: Uncommon: Angina pectoris
Musculoskeletal: Uncommon: Myalgia
Skin and appendages: Uncommon: Rash

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: Blood urea increased;
Uncommon: Hypercholesterolaemia, hyperlipaemia;
Rare: Hyperkalaemia
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
Immune system disorders: Anaphylactic reactions
Investigations: Hepatic enzymes increased, increased blood creatinine levels
Hepatobiliary disorders: Autoimmune hepatitis
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, exanthema, allergic dermatitis
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

Olmesartan medoxomil 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%).

Adverse events reported with olmesartan medoxomil monotherapy in the elderly with a greater than 1% incidence are shown in Table 3.

Table 3
Clinical adverse effects (all causalities) occurring in ≥1% of elderly patients

	Number (%) patients with adverse events	
Body system Adverse event	20 mg OM (n = 742)	40 mg OM (n = 464)
Gastrointestinal disorders		
Diarrhoea	7 (0.9%)	5 (1.1%)
Infections and infestations		
Bronchitis	3 (0.4%)	7 (1.5%)
Bronchitis acute	8 (1.1%)	2 (0.4%)
Influenza	9 (1.2%)	2 (0.4%)
Nasopharyngitis	16 (2.2%)	2 (0.4%)
Rhinitis	9 (1.2%)	2 (0.4%)
Urinary tract infection	10 (1.3%)	7 (1.5%)
Musculoskeletal and connective tissue disorders		
Arthralgia	10 (1.3%)	4 (0.9%)
Back pain	8 (1.1%)	1 (0.2%)
Nervous system disorders		
Dizziness	9 (1.2%)	8 (1.7%)
Headache	13 (1.8%)	13 (2.8%)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (1.1%)	6 (1.3%)

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

Paediatric Use

No clinically relevant differences were identified between the adverse experience profile for paediatric patients aged 1 to 18 years and that previously reported for adult patients.

In placebo-controlled period, the only adverse event that occurred in more than 2% of patients treated with olmesartan medoxomil and at a higher incidence versus placebo was pseudohyperkalaemia (Cohort A: 1.1% versus 2.3%; Cohort C: 0% versus 7.1%).

Clinical adverse effects (all causalities) occurring in ≥ 2% of patients aged 6-16 years (Cohorts A and B) and aged 1-5 years (Cohort C) versus placebo.

Table 4

	Number (%) patients with adverse event					
	Cohort A		Cohort B		Cohort C	
Body system Adverse event	OM (N = 93)	Placebo (N = 89)	OM (N = 53)	Placebo (N = 54)	OM (N = 29)	Placebo (N = 28)
Blood and lymphatic system disorders						
Eosinophilia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Gastrointestinal disorders						
Diarrhoea	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Vomiting	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions						
Pyrexia	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations						
Influenza	0 (0.0)	2 (2.3)	2 (3.8)	0 (0.0)	1 (3.5)	1 (3.6)
Nasopharyngitis	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (7.1)
Pharyngitis	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	1 (1.1)	2 (2.3)	0 (0.0)	0 (0.0)	1 (3.5)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Investigations						
Blood urea increased	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders						
Pseudohyperkalaemia	1 (1.1)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)
Nervous system disorders						
Dizziness	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Headache	7 (7.5)	3 (3.4)	3 (5.7)	1 (1.9)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders						
Cough	4 (4.3)	1 (1.1)	1 (1.9)	0 (0.0)	1 (3.5)	1 (3.6)
Pharyngolaryngeal pain	3 (3.2)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Rhinitis	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.9)	1 (3.5)	0 (0.0)
Rhinorrhoea	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders						
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.5)	0 (0.0)

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

Only limited information is available regarding overdosage in humans. The most likely effect of overdosage is hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of olmesartan.

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

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.

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

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

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

Clinical trials

The antihypertensive effects of olmesartan medoxomil 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 olmesartan medoxomil tended to increase with time and to increase with dose up to the 40 mg dose (refer Table 5). olmesartan medoxomil 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 $p<0.001$).

Table 5
Absolute reduction in mean systolic and diastolic BP[1] (mmHg)
(placebo-controlled studies)

Study (number of patients)	Placebo (n=543)	10 mg (n=521)	20 mg (n=513)	40 mg (n=195)	Time point
SE-866/06 (n=76)	-2.1/-3.2	—	-8.0/-7.1	—	6 weeks
866-204 (n=186)	0.0/-1.4	—	-12.8/-10.6	—	8 weeks
866-305 (n=517)	-2.1/-4.1	-14.6/-12.6	-13.1/-11.8	-17.3/-12.6	8 weeks
866-3062 (n=343)	-4.6/-7.0	-10.3/-8.3	-13.7/-9.2	—	8 weeks
SE-866/09 (n=790)	-9.1/-9.5	-17.1/-12.9	-18.4/-14.1	-20.6/-15.5	12 weeks
SE-866/10 (n=600)	-11.2/-10.2	-19.1/-15.9	-21.0/-16.8	—	12 weeks
SE-866/11 (n=287)	-4.0/-5.5	-13.2/-12.2	—	—	12 weeks

[1]Seated cuff blood pressure measurements; [2]This was a dose-titration study

Data above from seven placebo-controlled studies also confirm that the blood pressure lowering effect was maintained throughout the 24-hour period with olmesartan medoxomil once daily, with trough-to-peak ratios for systolic and diastolic response between 60 and 80%.

In a 4-month, open-label, extension study, all patients received 20 mg olmesartan medoxomil, which was titrated to 40 mg as required. If sitting diastolic blood pressure (sDBP) remained uncontrolled, hydrochlorothiazide 12.5-25 mg was then added. By Week 16, the majority of patients remained on 20 mg olmesartan medoxomil therapy (56.8%). Mean blood pressures generally continued to decrease in each treatment group from Week 4 to Week 16, as expected from the study design, which allowed treatment to be individually tailored to achieve blood pressure control (refer Table 6).

Table 6
Mean systolic and diastolic BP[1] (mmHg) values (open-label study)

Time point	Total number of patients	Systolic/diastolic BP (number of patients)			
		20 mg OM	40 mg OM	40 mg OM + 12.5 mg HCTZ	40 mg OM + 25 mg HCTZ
Week 4	n=399	142.6/91.8 (n=379)	155.8/100.8 (n=17)	155.0/95.5 (n=2)	146.0/101.0 (n=1)
Week 8	n=389	137.1/88.3 (n=273)	151.5/97.2 (n=93)	150.9/97.1 (n=19)	144.3/96.5 (n=4)
Week 12	n=381	135.1/86.1 (n=228)	146.0/93.2 (n=84)	147.4/93.9 (n=58)	141.8/91.3 (n=11)
Week 16	n=366	133.8/85.7 (n=208)	142.6/90.7 (n=68)	142.2/92.8 (n=63)	150.2/95.6 (n=27)

[1]Seated cuff blood pressure measurements; Abbreviations: OM – olmesartan medoxomil; HCTZ - hydrochlorothiazide

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

The antihypertensive effect of olmesartan medoxomil 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. Olmesartan medoxomil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

Use in elderly

The antihypertensive effects of olmesartan medoxomil 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 20 mg olmesartan medoxomil and if required, titrated to 40 mg after 4 weeks. If after 4 weeks on 40 mg olmesartan medoxomil target blood pressure was not achieved then hydrochlorothiazide was added. The results obtained for those on olmesartan medoxomil were similar to those in the losartan group.

Paediatric use

The antihypertensive effect of olmesartan medoxomil once daily was evaluated in a randomised, double-blind study involving 361 hypertensive paediatric patients (1-5 years n=59, 6-16 years n=302). Renal and urinary disorders with / without obesity were the most common underlying causes of hypertension in these patients enrolled in this study. Refer to Table 7 for a summary of the baseline demographic characteristics of study participants.

Table 7
Summary demographic and baseline characteristics

Parameter; mean (SD)	1-5 Year Age Group (n=60)	6-16 Year Age Group (n=302)
Age (years)	3.4 (1.45)	12.3 (2.85)
Height (cm)	98.3 (12.92)[1]	154.6 (17.79)
Weight (kg)	16.9 (6.61)[1]	71.1 (36.72)
Parameter; n (%)		
Race[2]		
White	27 (45.0)	119 (39.4)
Black/African heritage	7 (11.7)	147 (48.7)
Asian	21 (35.0)	19 (6.3)
Hawaiian	0 (0.0)	1 (0.3)
Other	5 (8.3)	26 (8.6)
Male	34 (56.7)	179 (59.3)
Primary Hypertension	20 (33.3)	225 (74.5)
Familial Hypertension	17 (28.3)	188 (62.3)

[1]n=59
[2]Patients were allowed to check more than one race

The study included three periods: a 3week double-blind, randomised, dose-response period for patients aged 6-16 years or, for patients aged 1-5 years, an open-label dose period; up to 2 week double-blind, randomised, placebo-controlled withdrawal period; and a 46 week open-label safety and efficacy period. The primary endpoints were the dose response in systolic blood pressure or in diastolic blood pressure for subjects 6 to 16 years of age at the end of this period. This study was not a clinical outcome study.

In the dose-response period, patients aged 6-16 years were randomised to receive either low or high dose of olmesartan medoxomil based on their weight. Patients weighing 20 to <35 kg received 2.5 mg (low) or 20 mg (high); those weighing ≥ 35 kg, received 5 mg (low) or 40 mg (high). Patients aged 1-5 years who weighed ≥ 5 kg received a dose of 0.3 mg/kg.

At the end of this period, olmesartan medoxomil reduced both systolic and diastolic blood pressure in a dose-dependent manner. In patients aged 6-16 years the low and high doses of olmesartan medoxomil significantly reduced systolic blood pressure by 6.63 and 11.87 mmHg from the baseline,

respectively. Patients aged 1-5 years of age had a clinically, and a statistically significant change from baseline reduction in systolic blood pressure of 13.31 mmHg.

In the placebo-controlled withdrawal period, patients who continued on olmesartan medoxomil had smaller increases in their systolic and diastolic blood pressure compared to patients switched to placebo. The difference between placebo and olmesartan medoxomil was statistically significant in patients aged 6-16 years, but was not statistically significant in patients aged 1-5 years. Refer to Table 8 for a summary of the mean change in SeSBP and SeDBP for both groups during the open-label (1-5 year age group)/double-blind (6-16 year age group) and placebo-controlled withdrawal periods of the study.

Table 8

Summary of mean change in SeSBP and SeDBP (mm Hg) during open-label (1-5 year age group)/double-blind (6-16 year age group) period and placebo-controlled withdrawal period

1-5 Year Age Group				
	SeSBP		SeDBP	
	Baseline BP[1] Mean (SD)	Change from baseline Mean (SD)	Baseline BP[1] Mean (SD)	Change from baseline Mean (SD)
Open-label period				
Olmesartan (n=59)	115.4 (8.62)	-13.31 (10.94)	72.6 (8.80)	-10.42 (9.78)
Placebo-controlled withdrawal period				
Olmesartan (n=29)	101.8 (11.87)	1.36 (8.99)	60.9 (9.16)	0.31 (8.56)
Placebo (n=28)	101.4 (10.09)	4.95 (8.57)	61.9 (8.56)	3.77 (7.20)
6-16 Year Age Group				
	SeSBP		SeDBP	
	Baseline BP[1] Mean (SD)	Change from baseline Mean (SD)	Baseline BP[1] Mean (SD)	Change from baseline Mean (SD)
Double-blind period				
Low dose Olmesartan (n=150)	130.4 (9.09)	-6.63 (10.17)	78.6 (8.53)	-4.76 (8.39)
High dose Olmesartan (n=150)	129.8 (8.98)	-11.87 (9.84)	77.4 (7.78)	-8.78 (9.22)
Placebo-controlled withdrawal period				
Olmesartan (n=145)	121.5 (12.66)	0.77 (9.45)	71.3 (9.70)	0.85 (7.79)
Placebo (n=141)	120.2 (13.00)	4.50 (9.75)	70.8 (10.42)	3.99 (9.63)

[1]Baseline at start of study period

At the end of the open-label efficacy and safety period, compared to baseline, the mean systolic and diastolic blood pressure were reduced at all visits for all patient age groups. However, data in children 1-5 years are limited due to small numbers of patients enrolled in the clinical studies. Overall, the clinical trials were unable to demonstrate that olmesartan medoxomil was significantly better than placebo in reducing blood pressure in children 1-5 years of age.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 has minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

Distribution

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 coadministered drugs is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible.

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.

Metabolism

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

Excretion

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.

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.

Paediatric

The single-dose pharmacokinetics of olmesartan was investigated in an open-label study in paediatric hypertensive patients aged 1 to 16 years. Refer to Table 9 for a summary of PK parameters. The clearance of olmesartan in paediatric patients was similar to that in adult patients when adjusted by body weight. There are, however, very limited data on the pharmacokinetics of olmesartan in children less than 6 years (see **Section 4.4 Special Warnings and Precautions for Use, Paediatric use**).

Table 9
Mean plasma pharmacokinetic parameters of olmesartan in paediatric hypertension patients[1]

Parameter; mean (SD)	6-12 Year Age Group (n=10)	13-16 Year Age Group (n=10)
C_{max} (ng/mL)	1227 (451)	895 (262)
AUC_{0-t} (ng/mL*hr)	7874 (2913)	5851 (2083)
$AUC_{0-\infty}$ (ng/mL*hr)	7988 (2913)	5982 (2130)
T_{max} (hr)	2.8 (1.3)	2.5 (1.1)
$t_{1/2}$ (hr)	8.4 (2.4)	9.1 (1.9)
CL/F (L/hr)	4.3 (1.9)	6.1 (2.6)

[1] Sample size insufficient to support calculation of summary statistics in 2-5 year age group (n=4)

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.

Renal impairment
In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared with subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <30 mL/min).

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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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. 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.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OLSETAN tablets also contain the following inactive ingredients: microcrystalline cellulose, hyprolose, lactose monohydrate, magnesium stearate, titanium dioxide and purified talc.

OLSETAN extemporaneous suspension contains additional inactive ingredients: purified water, Ora-Sweet® (syrup vehicle) and Ora-Plus® (suspending vehicle).

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

Tablets: Store below 25 °C.

Extemporaneous suspension: Store between 2-8 °C (Refrigerate; Do not freeze).
The suspension should be refrigerated at 2-8 °C (DO NOT FREEZE) and can be stored for up to 4 weeks.

Shake the suspension well before each use and return promptly to the refrigerator. An appropriate measuring device (syringe or measuring cup) should be used for the volume to be administered.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mg tablet: Blister pack of 30. Not currently available in Australia.

20 mg tablet: Blister pack of 30.

40 mg tablet: Blister pack of 30.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused suspension MUST be discarded after 28 days from the date of preparation.

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

6.7 PHYSICOCHEMICAL PROPERTIES

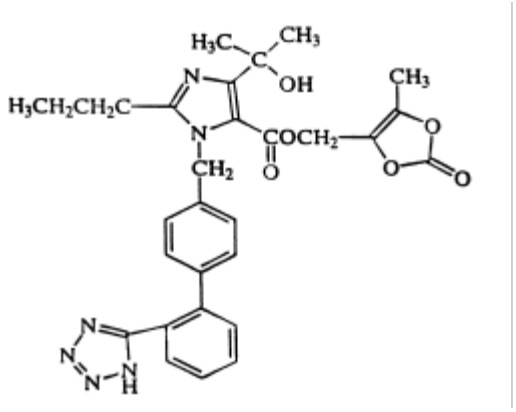
Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder. It is practically insoluble in water and sparingly soluble in methanol.

OLSETAN (olmesartan medoxomil), a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

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 $C_{29}H_{30}N_6O_6$. Its molecular weight is 558.59.

Chemical structure



CAS number 144689-63-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Accord Healthcare
Level 24, 570 Bourke Street
Melbourne VIC 3000
Australia
Phone: 1800 134 988
Email: ds@commercialeyes.com.au

9 DATE OF FIRST APPROVAL

19th May 2022

10 DATE OF REVISION

18th March 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Include autoimmune hepatitis as an adverse reaction in post-marketing experience subsection.