APPROVED PRODUCT INFORMATION

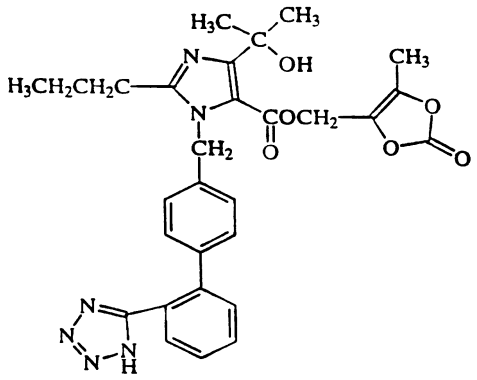
OLMESARTAN - MYL
(olmesartan medoxomil)

NAME OF THE MEDICINE

OLMESARTAN - MYL (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 (CAS no. 144689-63-4) 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 $C_{29}H_{30}N_6O_6$ and its structural formula is:



DESCRIPTION

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol. OLMESARTAN - MYL is available for oral use as film-coated tablets containing 20 mg or 40 mg olmesartan medoxomil. OLMESARTAN - MYL tablets also contain the following inactive ingredients: microcrystalline cellulose, low-substituted hydroxypropylcellulose, lactose, hydroxypropylcellulose, magnesium stearate, and Opadry OY-S-38956 that contains titanium dioxide, talc, and hydroxypropylmethylcellulose.

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

PHARMACOLOGY

Pharmacodynamics

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 AT1) 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 AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Angiotensin II plays a significant role in the pathophysiology of hypertension via the type 1 (AT1) receptor.

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

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

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

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

Pharmacokinetics

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.

Elimination

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 1 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 PRECAUTIONS, Paediatric Use).

Table 1. 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).

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 2). 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 2. 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
866-306[2] (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 3).

Table 3. 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 20mg olmesartan medoxomil and if required, titrated to 40mg after 4 weeks. If after 4 weeks on 40mg 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 4 for a summary of the baseline demographic characteristics of study participants.

Table 4. 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 3 week 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 5 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 5. 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 medoxomil (n=59)	115.4 (8.62)	-13.31 (10.94)	72.6 (8.80)	-10.42 (9.78)
Placebo-controlled withdrawal period				
olmesartan medoxomil (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 medoxomil (n=150)	130.4 (9.09)	-6.63 (10.17)	78.6 (8.53)	-4.76 (8.39)
High dose olmesartan medoxomil (n=150)	129.8 (8.98)	-11.87 (9.84)	77.4 (7.78)	-8.78 (9.22)
Placebo-controlled withdrawal period				
olmesartan medoxomil (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.

INDICATIONS

OLMESARTAN - MYL is indicated for the treatment of hypertension.

CONTRAINDICATIONS

OLMESARTAN - MYL is contraindicated in:

- Patients who are hypersensitive to either olmesartan medoxomil or any component of this medication.
- Pregnancy (see PRECAUTIONS, Use in pregnancy).
- Patients with severe renal impairment (creatinine clearance <30 mL/min) (see PRECAUTIONS, Renal impairment)
- Patients with severe hepatic impairment (Child-Pugh score 10 - 15) or biliary obstruction (see PRECAUTIONS, Hepatic impairment)
- Patients with diabetes who are taking aliskiren (see INTERACTIONS WITH OTHER MEDICINES)

PRECAUTIONS

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.

Renal impairment and kidney transplantation

When olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of OLMESARTAN - MYL is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min, eGFR <30 mL/min/1.73 m^2) (see DOSAGE AND ADMINISTRATION). There is no experience of the administration of OLMESARTAN - MYL 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.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child-Pugh score 10 - 15) and therefore use of OLMESARTAN - MYL in this patient group is not recommended (see DOSAGE AND ADMINISTRATION).

Hyperkalaemia

As with other angiotensin receptor antagonists and ACE inhibitors, hyperkalaemia may occur during treatment with OLMESARTAN - MYL, especially in the presence of renal impairment and/or heart failure. This is because OLMESARTAN - MYL contains olmesartan medoxomil, a drug which inhibits the renin-angiotensin system (RAS) and drugs that inhibit the RAS can cause hyperkalaemia. Close monitoring of serum potassium levels in at risk patients is recommended.

Lithium

As with other angiotensin receptor antagonists, the combination of lithium and OLMESARTAN - MYL is not recommended (see Interactions with other medicines).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy

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

Primary aldosteronism

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

Ethnic differences

As with all other angiotensin receptor antagonists, the blood pressure lowering effect of OLMESARTAN - MYL 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 OLMESARTAN - MYL 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. OLMESARTAN - MYL should be immediately discontinued in patients who develop angioedema, and OLMESARTAN - MYL 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.

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, OLMESARTAN - MYL 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 OLMESARTAN - MYL 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, OLMESARTAN - MYL 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 - MYL 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.

Paediatric use

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

Use in the elderly

Of the total number of hypertensive patients receiving OLMESARTAN - MYL 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.

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.

Effects on laboratory tests

Olmesartan medoxomil

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

Effects on ability to drive and use machines

The effect of OLMESARTAN - MYL 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.

INTERACTIONS WITH OTHER MEDICINES

Drugs that affect OLMESARTAN - MYL

Potassium supplements and potassium sparing diuretics

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

Other antihypertensive medications

The blood pressure lowering effect of OLMESARTAN - MYL 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 OLMESARTAN - MYL and other agents that affect the RAS.

Do not co-administer aliskiren with OLMESARTAN - MYL in patients with diabetes (see CONTRAINDICATIONS). Avoid use of aliskiren with OLMESARTAN - MYL 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 - MYL.

Drugs that are affected by OLMESARTAN - MYL

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 OLMESARTAN - MYL and lithium in combination is not recommended (see PRECAUTIONS, 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 - MYL 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.

ADVERSE EFFECTS

OLMESARTAN - MYL 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 - MYL 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 6:

Table 6. 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)

Body system Adverse event	Number (%) patients with adverse event			
	Placebo (n=555)	10 mg (n=528)	20 mg (n=566)	40 mg (n=195)
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
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 - MYL 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 7:

Table 7. 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 40mg 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.

	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)

DOSAGE AND ADMINISTRATION

Adults

Dosage must be individualised. The optimal recommended starting dose of OLMESARTAN - MYL 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 OLMESARTAN - MYL may be increased to a maximum of 40 mg daily.

OLMESARTAN - MYL may be administered with or without food. In order to assist compliance, it is recommended that OLMESARTAN - MYL 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.

Hydrochlorothiazde therapy should be considered in those patients requiring additional blood pressure control beyond 40 mg daily. OLMESARTAN - MYL 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 OLMESARTAN - MYL 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 PRECAUTIONS, Renal impairment and kidney transplantation). 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, OLMESARTAN - MYL should be administered under close medical supervision. In these patients a lower starting dose of 10 mg once daily[1] is recommended (see PRECAUTIONS, Intravascular volume depletion) (see PRESENTATIONS AND STORAGE CONDITIONS for marketed strengths).

If a patient becomes volume depleted whilst taking OLMESARTAN - MYL, 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 PRECAUTIONS, hepatic impairment).

If up-titration of OLMESARTAN - MYL 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 OLMESARTAN - MYL is based on age and/or weight (see Dosing recommendation table). If after 2 weeks of therapy further reduction in blood pressure is required, the dose of OLMESARTAN - MYL may be increased to a maximum of either 20 mg or 40 mg (see Dosing recommendation table). There are limited data available for the pharmacokinetics of olmesartan in children aged less than 6 years (see PHARMACOLOGY, Pharmacokinetics in special populations, *Paediatric*) and there are no pharmacokinetic data available in children with renal impairment (see DOSAGE AND ADMINISTRATION, Renal insufficiency).

[1] The OLMESARTAN - MYL 10 mg tablet is not currently registered in Australia

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* DOSAGE AND ADMINISTRATION, Special Populations, Preparation of 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. 240mL*.
* 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** OLMESARTAN - MYL **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.
The suspension cannot be prepared using water only and the tablets should not be ground before use. Only 20 mg OLMESARTAN - MYL tablets may be used in preparing the suspension. For handling and storage instruction, see PRESENTATION AND STORAGE CONDITIONS.

OVERDOSAGE

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 further advice on the management of an overdose contact the Poisons Information Centre (on 131126 in Australia).

PRESENTATION AND STORAGE CONDITIONS

A 10 mg tablet is not currently registered in Australia

20 mg tablet: White, circular film-coated tablet with C14 embossed on one side.
Blister pack of 30.

40 mg tablet: White, oval film-coated tablet with C15 embossed on one side.
Blister pack of 30.

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.

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

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ON ARTG)

7 June 2016

DATE OF MOST RECENT AMENDMENT

3 November 2016

Version 3.0

APPROVED PRODUCT INFORMATION

OLMESARTAN HCT - MYL
(olmesartan medoxomil/hydrochlorothiazide)

OLMESARTAN HCT - MYL 20/12.5 mg
OLMESARTAN HCT - MYL 40/12.5 mg
OLMESARTAN HCT - MYL 40/25 mg

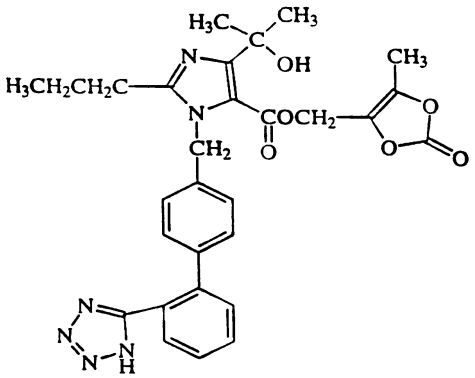
NAME OF THE MEDICINE

OLMESARTAN HCT - MYL consists of olmesartan medoxomil and hydrochlorothiazide (HCTZ).

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.

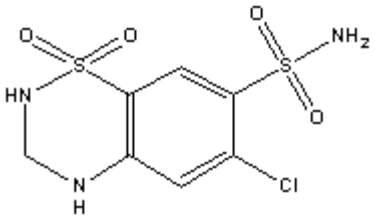
Olmesartan medoxomil (CAS no. 144689-63-4) is described chemically as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate.

Its empirical formula is $C_{29}H_{30}N_6O_6$ and its structural formula is:



HCTZ (CAS no. 58-93-5) is described chemically as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

The empirical formula is $C_7H_8ClN_3O_4S_2$ and the structural formula is:



DESCRIPTION

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol.

HCTZ is a white, or almost white, crystalline powder, with a molecular weight of 297.7. HCTZ is very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

OLMESARTAN HCT - MYL is available for oral use as film-coated tablets containing 20/12.5 mg, 40/12.5 mg, or 40/25 mg olmesartan medoxomil/HCTZ. OLMESARTAN HCT - MYL tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose, hydroxypropylcellulose, magnesium stearate, and Opadry O2A22352 or Opadry O2A24576. These contain titanium dioxide, purified talc, hypromellose, and iron oxides.

PHARMACOLOGY

Pharmacodynamics

OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL 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 (≤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.

Pharmacokinetics

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 elimination

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 DOSAGE AND 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 DOSAGE AND ADMINISTRATION and PRECAUTIONS, Renal insufficiency).

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 DOSAGE AND ADMINISTRATION and PRECAUTIONS).

CLINICAL TRIALS

Olmesartan medoxomil

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. 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 $p<0.001$). 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%.

The blood pressure lowering effect of olmesartan medoxomil, 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 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 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 2 below).

Table 1. 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 olmesartan medoxomil/HCTZ 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 olmesartan medoxomil. At 4 week intervals, the treatment was titrated to achieve target BP. The results obtained for those on olmesartan medoxomil/HCTZ were similar to those in the losartan group.

INDICATIONS

Treatment of hypertension.

Treatment should not be initiated with this fixed dose combination.

CONTRAINDICATIONS

OLMESARTAN HCT - MYL 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 PRECAUTIONS, Use in pregnancy)
- Patients with anuria or severe renal impairment (creatinine clearance <30 mL/min) (see PRECAUTIONS, Renal impairment)
- Patients with severe hepatic impairment (Child-Pugh score 10 - 15), cholestasis or biliary obstruction (see PRECAUTIONS, Hepatic impairment)
- Patients who are breastfeeding

- Patients with refractory hypokalaemia, hypercalcaemia, hyponatraemia, and symptomatic hyperuricaemia (see PRECAUTIONS, Electrolyte imbalance)
- Patients with diabetes who are taking aliskiren (see INTERACTIONS WITH OTHER MEDICINES)

PRECAUTIONS

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 HCT - MYL.

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.

Renal impairment and kidney transplantation

OLMESARTAN HCT - MYL should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) (see DOSAGE AND 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 OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL in patients with recent kidney transplantation.

The pharmacokinetics of OLMESARTAN HCT - MYL or coadministered olmesartan medoxomil and HCTZ have not been studied in patients with 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 OLMESARTAN HCT - MYL in cases where no other etiology is identified.

Hepatic impairment

OLMESARTAN HCT - MYL 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 CONTRAINDICATIONS).

The pharmacokinetics of OLMESARTAN HCT - MYL or coadministered olmesartan medoxomil and HCTZ have not been studied in patients with hepatic impairment.

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 OLMESARTAN HCT - MYL 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 Interactions with other medicines). 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, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see ADVERSE 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 OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL (see Interactions with other medicines).

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

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with OLMESARTAN HCT - MYL, 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 OLMESARTAN HCT - MYL and lithium is not recommended (see Interactions with other medicines).

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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.

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.

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.

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, OLMESARTAN HCT - MYL 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, OLMESARTAN HCT - MYL 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, OLMESARTAN HCT - MYL 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 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 $\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.

Paediatric use

The safety and effectiveness of OLMESARTAN HCT - MYL in children have not been established.

Use in the elderly

Clinical Studies of OLMESARTAN HCT - MYL 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.

Effect 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.

Effects on ability to drive and use machines

The effect of OLMESARTAN HCT - MYL 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.

INTERACTIONS WITH OTHER MEDICINES

Effects of other medicinal products on OLMESARTAN HCT - MYL

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) may lead to increases in serum potassium (see PRECAUTIONS).

If drugs which affect potassium levels are to be prescribed in combination with OLMESARTAN HCT - MYL, monitoring of potassium plasma levels is advised.

Other antihypertensive medications

The blood pressure lowering effect of OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL and other agents that affect the RAS.

Do not co-administer aliskiren with OLMESARTAN HCT - MYL in patients with diabetes (see CONTRAINDICATIONS). Avoid use of aliskiren with OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL 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 PRECAUTIONS, 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 OLMESARTAN HCT - MYL 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.

ADVERSE 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 OLMESARTAN HCT - MYL 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 2:

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

Body system Adverse event	Number (%) patients with adverse event			
	Olmesartan medoxomil/ HCTZ (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)
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
Metabolism and nutrition disorders: 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

OLMESARTAN HCT - MYL 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 3:

Table 3. 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%)
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 OLMESARTAN HCT - MYL, 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
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

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%)

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 PRECAUTIONS).

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

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 (including pneumonitis and pulmonary oedema*),* dyspnoea, interstitial pneumonia
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)

DOSAGE AND ADMINISTRATION

Adults

OLMESARTAN HCT - MYL is administered once daily, with or without food, in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or HCTZ alone.

OLMESARTAN HCT - MYL is registered in combinations of 20/12.5 mg, 40/12.5 mg and 40/25 mg (See Presentation and Storage Conditions 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 olmesartan medoxomil 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 olmesartan medoxomil 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 OLMESARTAN HCT - MYL 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 OLMESARTAN HCT - MYL is used in such patients, periodic monitoring of renal function is advised (see PRECAUTIONS). OLMESARTAN HCT - MYL is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) (see CONTRAINDICATIONS).

Intravascular volume depletion

For patients with possible depletion of intravascular volume, particularly those with impaired renal function, OLMESARTAN HCT - MYL should be administered under close medical supervision.

If a patient becomes volume depleted whilst taking OLMESARTAN HCT - MYL, 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 PRECAUTIONS, hepatic impairment).

OLMESARTAN HCT - MYL should not be used in patients with severe hepatic impairment, cholestasis and biliary obstruction (see 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 OLMESARTAN HCT - MYL in children have not been established.

OVERDOSAGE

No specific information is available on the effects or treatment of OLMESARTAN HCT - MYL 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 further advice on the management of an overdose contact the Poisons Information Centre.

PRESENTATION AND STORAGE CONDITIONS

OLMESARTAN HCT - MYL 20/12.5 mg contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide. It is a round tablet, approximately 8.5 mm in diameter, reddish yellow in colour with C22 debossed on one side.

OLMESARTAN HCT - MYL 40/12.5 mg contains 40 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide. It is an oval tablet, approximately 15 mm x 7 mm, reddish yellow in colour with C23 debossed on one side.

OLMESARTAN HCT - MYL 40/25 mg contains 40 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide. It is an oval tablet, approximately 15 mm x 7 mm in diameter, pinkish in colour with C25 debossed on one side.

OLMESARTAN HCT - MYL is available in blister packs of 10 and 30 film-coated tablets.

Not all pack sizes may be available.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 7 June 2016

DATE OF MOST RECENT AMENDMENT

3 November 2016

Version 3.0