AUSTRALIAN PRODUCT INFORMATION
SEVIKAR®
(olmesartan medoxomil and amlodipine as besilate) Tablets

1   NAME OF THE MEDICINE

Olmesartan medoxomil and amlodipine as besilate

2   QUALITATIVE AND QUANTITATIVE COMPOSITION

SEVIKAR 20/5 contains 20 mg of olmesartan medoxomil and amlodipine 5 mg as besilate.

SEVIKAR 20/10 contains 20 mg of olmesartan medoxomil and amlodipine 10 mg as besilate.

SEVIKAR 40/5 contains 40 mg of olmesartan medoxomil and amlodipine 5 mg as besilate.

SEVIKAR 40/10 contains 40 mg of olmesartan medoxomil and amlodipine 10 mg as besilate.

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

Amlodipine besilate is a white crystalline powder, slightly soluble in water and sparingly soluble in ethanol.

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

3   PHARMACEUTICAL FORM

SEVIKAR 20/5 is a round tablet, approximately 6 mm in diameter, white in colour with C73 debossed on one side.

SEVIKAR 20/10 is a round tablet, approximately 8 mm in diameter, greyish-orange in colour with C74 debossed on one side. (Not currently available in Australia).

SEVIKAR 40/5 is a round tablet, approximately 8 mm in diameter, cream in colour with C75 debossed on one side.

SEVIKAR 40/10 is a round tablet, approximately 8 mm in diameter, brownish red in colour with C77 debossed on one side.

4   CLINICAL PARTICULARS

4.1   THERAPEUTIC INDICATIONS

SEVIKAR is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination (see **Section 4.2 Dose and Method of Administration**).

4.2   DOSE AND METHOD OF ADMINISTRATION

SEVIKAR is registered in four strengths: SEVIKAR 20/5 (olmesartan medoxomil 20 mg and amlodipine as besilate 5 mg); SEVIKAR 20/10 (olmesartan medoxomil 20 mg and amlodipine as besilate 10 mg); SEVIKAR 40/5 (olmesartan medoxomil 40 mg and amlodipine as besilate 5 mg); SEVIKAR 40/10 (olmesartan medoxomil 40 mg and amlodipine as besilate 10 mg). (See **Section 6.5 Nature and Contents of Container** for marketed strengths).

Usual adult dose

The recommended dosage of SEVIKAR is one tablet daily, with or without food. Treatment should not be initiated with this combination.

Replacement therapy

For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to SEVIKAR tablets containing the same component doses.

Add-on therapy

For patients whose blood pressure is not adequately controlled on either olmesartan or amlodipine monotherapy, they may be switched to combination therapy with SEVIKAR. Titration of the dosage is recommended. For patients whose blood pressure is not adequately controlled on SEVIKAR 20/5, then titration to SEVIKAR 40/5 is recommended. Subsequently, if the patient's blood pressure is not adequately controlled on SEVIKAR 40/5, then titration to SEVIKAR 40/10 is recommended.

For patients whose blood pressure is not adequately controlled on SEVIKAR 40/10, it may be possible to add a thiazide diuretic (see **Section 4.4 Special Warnings and Precautions for Use, Intravascular volume depletion**, and **Concomitant use of ACE inhibitors or angiotensin receptor antagonists and anti-inflammatory drugs and thiazide diuretics**).

Consult the Product Information of the individual thiazide diuretic being used and this Product Information prior to adding a thiazide diuretic to SEVIKAR therapy.

Elderly

No adjustment of the recommended dose is generally required for elderly patients.

Renal impairment

No adjustment of the recommended dose is required for patients with mild to moderate impairment of renal function. The use of SEVIKAR in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended (see **Section 4.3 Contraindications**).

Hepatic impairment

SEVIKAR should be used with caution in patients with mild to moderate hepatic impairment. SEVIKAR is not recommended in patients with severe hepatic impairment and biliary obstruction (see **Section 4.3 Contraindications**).

Children and adolescents

SEVIKAR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy.

4.3   CONTRAINDICATIONS

SEVIKAR is contraindicated in:

- Patients who are hypersensitive to any component of the tablet or to dihydropyridines
- Pregnancy (see **Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy**)
- Patients with severe renal impairment (see **Section 4.4 Special Warnings and Precautions for Use, Use in renal impairment**)
- Patients with severe hepatic impairment or biliary obstruction (see **Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment**)

- Patients with diabetes who are taking aliskiren (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Due to the component amlodipine, SEVIKAR is also contraindicated in:

- Cardiogenic shock
- Acute myocardial infarction (within the first 4 weeks)
- Unstable angina pectoris

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravascular volume depletion

Symptomatic hypotension may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting, especially after receiving the first dose. Correction of this condition prior to administration of SEVIKAR, or close medical supervision at the start of treatment, is recommended.

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

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system, such as angiotensin II receptor antagonists, has been associated with acute hypotension, azotemia, oliguria, or rarely, acute renal failure and/or death.

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.

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 SEVIKAR in cases where no other etiology is identified.

Hyperkalaemia

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

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy

As with all 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 SEVIKAR is not recommended in such patients.

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

Increased angina and/or myocardial infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Congestive heart failure

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. SEVIKAR has not been studied in patients with heart failure.

In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-blocker withdrawal

Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Peripheral oedema

Mild to moderate peripheral oedema was the most common adverse event in the clinical trials with amlodipine. The incidence of peripheral oedema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

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.

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.

Lithium

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

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.

General

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

Use in hepatic impairment

Since amlodipine is extensively metabolized by the liver, exposure to amlodipine and olmesartan is increased in patients with hepatic impairment. Care should be taken when SEVIKAR is administered in patients with mild to moderate hepatic impairment. Use of SEVIKAR in patients with severe hepatic impairment is not recommended.

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine should therefore be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **Section 4.2 Dose and Method of Administration**).

Use in renal impairment

When SEVIKAR is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of SEVIKAR is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min) (see **Section 4.3 Contraindications**). There is no experience of the administration of SEVIKAR in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance <12 mL/min).

Use in the elderly

See **Section 4.2 Dose and Method of Administration** and **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations**.

Paediatric use

SEVIKAR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy.

Effects on laboratory tests

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

Amlodipine
Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine or liver function tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

SEVIKAR

No drug interaction studies have been conducted with SEVIKAR and other drugs; although, studies have been conducted with the individual olmesartan medoxomil and amlodipine components of SEVIKAR, as described below.

Olmesartan medoxomil

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

Other antihypertensive medications
The blood pressure lowering effect of olmesartan medoxomil 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 (see **Section 4.4 Special Warnings and Precautions for Use**).

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 SEVIKAR and other agents that affect the RAS.

Do not co-administer aliskiren with SEVIKAR in patients with diabetes (see **Section 4.3 Contraindications**). Avoid use of aliskiren with SEVIKAR 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.

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 medoxomil and lithium in combination is not recommended (see **Section 4.4 Special Warnings and Precautions for Use, Lithium**). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

Olmesartan medoxomil 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 medoxomil and drugs metabolised by the above cytochrome P450 enzymes are expected.

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

Amlodipine

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Special studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time. *In vitro* data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin).

Grapefruit juice
Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients, the plasma concentration of amlodipine was increased. The clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 inducers

There are no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum* (St John's Wort)) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil

A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin

Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Ethanol (alcohol)

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Ciclosporin

In a prospective study in renal transplant patients (N=11), an average 40% increase in trough ciclosporin levels was observed in the presence of amlodipine. The co-administration of amlodipine with ciclosporin may increase exposure to ciclosporin. As SEVIKAR contains amlodipine, the monitoring of trough ciclosporin levels during concomitant use is recommended and dose adjustment of ciclosporin should be made as necessary.

Tacrolimus

The co-administration of amlodipine with tacrolimus may increase exposure of tacrolimus. As SEVIKAR contains amlodipine, the monitoring of tacrolimus blood levels during concomitant use is recommended and dose adjustment of tacrolimus should be made as necessary.

4.6   FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of the olmesartan medoxomil/amlodipine combination on fertility have not been evaluated in animal studies.

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (about 240 times the MRHD of 40 mg/day on a mg/m^2 basis) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

Use in pregnancy

(Category D)

SEVIKAR can cause foetal harm when administered to a pregnant woman. As a precaution, SEVIKAR must not be used during the first trimester of pregnancy. The patient should change to an appropriate alternative form of medication before a planned pregnancy. If pregnancy occurs during therapy, SEVIKAR must be discontinued as soon as possible. There is no experience of the use of SEVIKAR in pregnant women.

If SEVIKAR is used during pregnancy, or if the patient becomes pregnant while taking SEVIKAR, the patient should be apprised of the potential hazard to a foetus. Should exposure to SEVIKAR have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended. Newborns exposed to angiotensin II antagonists *in utero* must be closely monitored for the occurrence of hypotension, oliguria, and hyperkalaemia.

No animal reproductive toxicity studies have been performed with the combination of olmesartan medoxomil and amlodipine.

Olmesartan medoxomil
Olmesartan medoxomil is contraindicated in the second and third trimesters of pregnancy. During the second and third trimesters of pregnancy, substances that act on the renin-angiotensin system may cause damage (hypotension, impairment of renal function, oligouria and/or anuria, oligohydramnia, cranial hypoplasia, intrauterine growth retardation) and death in foetuses and neonates. Cases of pulmonary hypoplasia, facial anomalies and contractions of limbs were also reported. Animal experimental studies with olmesartan medoxomil have shown furthermore that renal damage may occur in the late foetal and neonatal phase.

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

Amlodipine
Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

In animal studies, amlodipine was not teratogenic in rats (18 mg/kg/day) or rabbits (10 mg/kg/day). Amlodipine (10 mg/kg/day as besilate salt, 7 mg/kg/day base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

Use in lactation

It is not known whether the olmesartan medoxomil or amlodipine components of SEVIKAR are excreted in human milk, but olmesartan is excreted into the milk of lactating rats and calcium channel blockers of the dihydropyridine type are excreted in breast milk. Because of

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, it should be borne in mind that dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of SEVIKAR was investigated in controlled clinical trials in 2892 patients receiving olmesartan medoxomil in combination with amlodipine.

Table 1 summarises the most common (≥ 1% in any group) drug-related adverse events by system organ class and preferred term. The profile of drug-related adverse events was similar across the treatments, most commonly general disorders and administration site conditions, nervous system or vascular adverse events.

Table 1
Drug-related adverse events with ≥ 1% incidence in any combined treatment group –
Phase III all patients cohort

Number of patients with (%)	OM/AML (N=2892)	OM (N=663)	AML (N=512)	Placebo (N=162)
General Disorders and Administration Site Conditions				
Oedema peripheral	252 (8.7)	35 (5.3)	45 (8.8)	9 (5.6)
Oedema	82 (2.8)	9 (1.4)	15 (2.9)	2 (1.2)
Fatigue	46 (1.6)	13 (2.0)	5 (1.0)	5 (3.1)
Pitting oedema	37 (1.3)	6 (0.9)	4 (0.8)	2 (1.2)
Nervous System Disorders				
Dizziness	80 (2.8)	19 (2.9)	6 (1.2)	6 (3.7)
Headache	68 (2.4)	26 (3.9)	8 (1.6)	11 (6.8)
Vascular Disorders				
Hypertension	2 (0.1)	5 (0.8)	0 (0.0)	7 (4.3)
Gastrointestinal Disorders				
Nausea	12 (0.4)	2 (0.3)	2 (0.4)	3 (1.9)

Adverse events are listed below by system organ class. Frequencies are defined as: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Cardiac disorders: Uncommon: Palpitations, Tachycardia

Ear and labyrinth disorders: Uncommon: Vertigo

Gastro-intestinal disorders: Uncommon: Nausea, vomiting, dyspepsia, diarrhoea, constipation, dry mouth, upper abdominal pain

General disorders and administration site conditions: Uncommon: Asthenia

Rare: Face oedema

Immune system disorders: Rare: Drug hypersensitivity

Infections and infestations: Common: Upper respiratory tract infection

Investigations:	Uncommon: Blood potassium decreased, blood creatinine increased, blood uric acid increased, gamma glutamyl transferase increased
Metabolism and nutrition disorders:	Uncommon: Hyperkalaemia
Musculoskeletal and connective tissue disorders:	Uncommon: Muscle spasm, pain in extremity, back pain
Nervous system disorders:	Uncommon: Postural dizziness, lethargy, paraesthesia, hypoaesthesia
	Rare: Syncope
Psychiatric disorders:	Uncommon: Libido decreased, anxiety
Renal and urinary disorders:	Uncommon: Pollakiuria
Reproductive system and breast disorders:	Uncommon: Erectile dysfunction
Respiratory, thoracic and mediastinal disorders:	Uncommon: Dyspnoea, cough
Skin and subcutaneous tissue disorders:	Uncommon: Rash
	Rare: Urticaria
Vascular disorders:	Uncommon: Hypotension, orthostatic hypotension

Oedema

Oedema is a known dose-dependent undesirable effect of amlodipine but not of olmesartan medoxomil. The incidence of oedema was significantly lower in patients receiving SEVIKAR than in those who received amlodipine 10 mg alone. Across all treatment groups, the frequency of oedema was generally higher in women than in men.

Additional information on the individual components

Adverse events previously reported with one of the individual components may be potential adverse events with SEVIKAR, 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 effects 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; sprue-like enteropathy, diarrhoea
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)).

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials worldwide. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%).

The most common side effects are headache and oedema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Table 2

Adverse Event	2.5 mg n=275	5.0 mg n=296	10.0 mg n=268	Placebo n=520
Oedema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo controlled clinical trials include the following:

Table 3

	Placebo controlled studies	
Adverse Event	Amlodipine (%) n=1730	Placebo (%) n=1250
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in ≤ 1% but > 0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Autonomic Nervous System: Dry mouth, sweating increased

Cardiovascular: Hypotension, angina pectoris, myocardial infarction

Central and Peripheral Nervous System: Hypoesthesia, paraesthesia, tremor, peripheral neuropathy, dysgeusia, syncope, postural dizziness

Endocrine: Gynaecomastia

Gastrointestinal:	Constipation, dyspepsia, dysphagia, diarrhoea, flatulence, vomiting, altered bowel habits, pancreatitis, gingival hyperplasia
General:	Allergic reactions, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, hyperhidrosis
Heart Rate and Rhythm Disorders:	Tachycardia
Metabolic and Nutritional:	Anorexia, thirst, hyperglycaemia
Musculoskeletal System:	Arthralgia, arthrosis, myalgia, ankle swelling, muscle spasm
Platelet, Bleeding & Clotting:	Thrombocytopenia
Psychiatric:	Sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalisation, mood changes, confusion, irritability, insomnia
Respiratory System:	Dyspnoea, epistaxis
Skin and Appendages:	Angioedema, alopecia, pruritus, rash, rash erythematous, rash maculopapular, exanthema, purpura
Special Senses:	Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus, vertigo, blurred vision
Urinary System:	Micturition frequency, micturition disorder, nocturia
Vascular (extracardiac):	Vasculitis, postural hypotension, peripheral ischaemia
White Blood Cell:	Leucopenia

These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in multiple dose studies.

The following events occurred in ≤ 0.1% of patients: exfoliative dermatitis, photosensitivity, Stevens-Johnson syndrome, cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, dermatitis, erythema multiforme, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, xerophthalmia and weight decrease.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain. There have been post-marketing reports of extrapyramidal disorder in association with use of amlodipine.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9   OVERDOSE

Symptoms

There is no experience of overdose in humans with SEVIKAR. The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred. Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.

Treatment

In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.

Clinically significant hypotension due to an overdose of SEVIKAR requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan is unknown.

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

5   PHARMACOLOGICAL PROPERTIES

5.1   PHARMACODYNAMIC PROPERTIES

Mechanism of action

SEVIKAR is a combination of two antihypertensive drugs: olmesartan medoxomil, an angiotensin receptor blocker and amlodipine besilate, a dihydropyridine calcium channel blocker. The combination of these active ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

The olmesartan medoxomil component of SEVIKAR blocks the vasoconstrictor effects of angiotensin II and the amlodipine component of SEVIKAR inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

Olmesartan medoxomil
Angiotensin II is formed from angiotensin I in a reaction catalysed 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 AT1 receptor than for the AT2 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. The effect of olmesartan on mortality and morbidity is not yet known.

Amlodipine

Experimental data suggests that amlodipine binds to both dihydropyridine and nonhydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel is characterised by a gradual rate of association and dissociation with the binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/ -2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Clinical trials

In three clinical trials involving hypertensive adults with a mean sitting diastolic BP between 95 mmHg and 120 mmHg, over 2000 hypertensive patients received SEVIKAR. In a placebo

controlled clinical trial with over 600 patients and in 2 active control clinical trials, over 700 hypertensive patients received SEVIKAR once daily. Exclusion criteria for the trials included the contraindications listed in the PI, and the conditions listed in the precautions. Patients with secondary hypertension, uncontrolled diabetes, evidence of ECG changes requiring treatment, known malabsorption or significant increases in liver enzymes were also excluded. No trials assessing the long-term effects on cardiovascular morbidity or mortality have been conducted with SEVIKAR.

Initial therapy (study 301)

In a double-blind, randomised, placebo controlled, factorial designed study, 1923 mild to severe hypertensive patients were randomised to receive either: placebo, olmesartan medoxomil (10, 20 or 40 mg), amlodipine (5 or 10 mg) or the combination of olmesartan medoxomil and amlodipine (10/5, 10/10, 20/5, 20/10, 40/5, or 40/10) for 8 weeks. SEVIKAR produced the greatest mean change in diastolic and systolic blood pressure in comparison to the monotherapy and placebo (tables 4 and 5). The highest mean change in blood pressure was observed for the highest dose of SEVIKAR (40/10 mg; -30.1/-19.0 mmHg). The mean change in diastolic and systolic blood pressure was dose dependent.

Table 4
Mean change in diastolic BP (mmHg) from baseline at week 8
[Mean baseline DBP was 102 mmHg]

Amlodipine	Olmesartan medoxomil			
	0	10	20	40
0	-3.1	-8.3	-9.2	-10.2
5	-9.4	-13.8	-14.0	-15.5
10	-12.7	-16.0	-17.0	-19.0

Table 5
Mean change in systolic BP (mmHg) from baseline at week 8
[Mean baseline SBP was 164 mmHg]

Amlodipine	Olmesartan medoxomil			
	0	10	20	40
0	-4.8	-11.5	-13.8	-16.1
5	-14.9	-24.2	-23.6	-25.4
10	-19.7	-25.3	-29.2	-30.1

The proportion of patients that achieved blood pressure goal of < 140/90 mmHg (or < 130/80 mmHg for diabetics) were higher for those on SEVIKAR in comparison to those on the individual monotherapy (Table 6).

Table 6
Proportion of patients who achieved blood pressure goal* at week 8

Amlodipine	Olmesartan medoxomil			
	0	10	20	40
0	8.8	20.0	26.4	36.3
5	21.1	35.0	42.5	51.0
10	32.5	49.1	53.2	49.1

* defined as < 140/90 mmHg, or < 130/80 mmHg for diabetics

Add-on therapy (Studies 302 and 303)

Two double-blind, randomised, active-controlled studies were conducted in patients with moderate to severe hypertension. These studies evaluated the effectiveness of add-on

therapy for these patients whose BP was not adequately controlled following 8 weeks of monotherapy of either 20 mg of olmesartan medoxomil or 5 mg of amlodipine.

Olmesartan medoxomil with amlodipine add-on therapy (study 302)

In study 302, 538 moderate to severe hypertensive patients whose blood pressure was inadequately controlled after 8 weeks of 20 mg olmesartan medoxomil monotherapy, were randomised to receive either: placebo or amlodipine (5 mg or 10 mg) as add-on therapy to the olmesartan medoxomil 20 mg for another 8 weeks. The mean change of DBP and SBP was significantly greater for patients who were on SEVIKAR (both 20/5 and 20/10) compared to olmesartan medoxomil (20 mg) monotherapy (p<0.001) (Table 7).

Table 7
Mean change in DBP and SBP at week 8 [mean baseline BP 171/104 mmHg]

	Olmesartan medoxomil 20 mg + Placebo (N = 179)	SEVIKAR 20/5 (N = 182)	SEVIKAR 20/10 (N = 177)
Seated DBP (mmHg) Mean change (SD)	- 7.8 (7.86)	- 10.6 (7.20)	- 11.1 (8.01)
Seated SBP (mmHg) Mean change (SD)	- 10.6 (12.89)	- 16.2 (10.66)	- 16.5 (12.93)

Significantly more patients on the combination of olmesartan medoxomil with amlodipine (SEVIKAR 20/5 and SEVIKAR 20/10) achieved BP goal (< 140/90 mmHg or < 130/80 mmHg for diabetic patients) compared to 20 mg olmesartan medoxomil alone (SEVIKAR 20/10; 45.8%, SEVIKAR 20/5; 44.5% and olmesartan medoxomil 28.5%; p<0.0011).

Amlodipine with olmesartan medoxomil add-on therapy (study 303)

In study 303, 755 patients whose blood pressure was inadequately controlled after 8 weeks of 5 mg amlodipine monotherapy, were randomised to receive either: placebo or olmesartan medoxomil (20 mg or 40 mg) as add-on therapy to amlodipine 5 mg. The mean change of DBP and SBP was significantly greater for patients who were on SEVIKAR (both 20/5 and 40/5) compared to amlodipine (5 mg) monotherapy (p<0.0001) (Table 8).

Table 8
Mean change in DBP and SBP at week 8 [mean baseline BP 64/102 mmHg]

	Amlodipine 5 mg + Placebo (N = 184)	SEVIKAR 20/5 (N = 187)	SEVIKAR 40/5 (N = 186)
Seated DBP (mmHg) Mean change (SD)	- 5.7 (7.66)	- 9.3 (7.74)	- 9.5 (6.64)
Seated SBP (mmHg) Mean change (SD)	- 9.9 (12.43)	- 15.3 (13.32)	- 16.7 (12.00)

Significantly more patients on the combination of olmesartan medoxomil with amlodipine (SEVIKAR 20/5 and SEVIKAR 40/5) achieved BP goal (< 140/90 mmHg or < 130/80 mmHg for diabetic patients) compared to 5 mg olmesartan medoxomil alone (SEVIKAR 20/5, 53.5%; SEVIKAR 40/5, 50.5% and amlodipine, 29.9%; p<0.0001).

The three studies performed confirmed that the blood pressure lowering effect of SEVIKAR once daily was maintained throughout the 24-hour dose interval, with trough-to-peak ratios of 71% to 82% for systolic and diastolic response and with 24-hour effectiveness being confirmed by ambulatory blood pressure monitoring.

The antihypertensive effect of SEVIKAR was similar irrespective of age and gender, and was similar in patients with and without diabetes.

In two open-labelled, non-randomised extension studies (studies 301 and 303), the antihypertensive effect of SEVIKAR 40/5 was sustained during long-term therapy. When required in patients whose BP was not adequately controlled on the highest available dose of SEVIKAR 40/10, the addition of a diuretic (hydrochlorothiazide) increased the blood pressure lowering effect of SEVIKAR.

Olmesartan medoxomil (active ingredient of SEVIKAR)

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 $p<0.001$).

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%.

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 had an additional blood pressure lowering effect when added to hydrochlorothiazide.

Amlodipine (active ingredient of SEVIKAR)

In patients with hypertension once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval postdose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24 hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to 1 year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

5.2   PHARMACOKINETIC PROPERTIES

Following oral intake of SEVIKAR, peak plasma concentrations of olmesartan and amlodipine are reached at 1.5 – 2 hours and 6 – 8 hours, respectively. The rate and extent of absorption of the two active substances from SEVIKAR are equivalent to the rate and extent of absorption following intake of the two components as separate tablets. Food does not affect the bioavailability of olmesartan medoxomil and amlodipine from SEVIKAR.

Olmesartan medoxomil

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 medoxomil 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 has minimal effect on the bioavailability of olmesartan medoxomil 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 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.

Metabolism and excretion
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. Steady state was reached after the first few doses and no further accumulation was evident within 14 days of repeated dosing. Renal clearance was approximately 0.5–0.7 L/h and was independent of dose.

Amlodipine

Absorption
After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability is estimated as between 64% and 90%. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2-8 hours) in patients with hepatic insufficiency. The bioavailability of amlodipine is not altered by the presence of food.

Distribution
The volume of distribution is approximately 20 L/kg. The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

Metabolism and excretion
Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Pharmacokinetics in special populations

Elderly
The pharmacokinetic properties of SEVIKAR in the elderly are similar to those of the individual components.

Olmesartan medoxomil
In hypertensive patients, the AUC at steady state was increased by approximately 35% in elderly patients (65–75 years old) and by approximately 44% in very elderly patients (≥75 years old) compared with the younger age group.

Amlodipine
In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

Paediatric
No pharmacokinetic data in paediatric patients for SEVIKAR are available.

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

Amlodipine
No pharmacokinetic data for amlodipine in paediatric patients are available.

Gender
Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. Gender had no effect on the clearance of amlodipine.

Olmesartan medoxomil
Minor differences were observed in the pharmacokinetics of olmesartan medoxomil in women compared to men. AUC and C_{max} were 10% to 15% higher in women than in men.

Renal impairment

Olmesartan medoxomil
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 < 20 mL/min). The pharmacokinetics of olmesartan medoxomil in patients undergoing haemodialysis have not been studied.

Amlodipine
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Hepatic insufficiency

Olmesartan medoxomil
Mean olmesartan AUC after single oral administration to patients with moderate hepatic impairment was increased by about 48% compared with healthy controls (total group), or by about 60% when compared with matched controls only. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.

Amlodipine
Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine therefore should be administered with caution in these patients and careful monitoring should be performed.

Heart failure

Amlodipine
Patients with heart failure have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

5.3   PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with the olmesartan medoxomil/amlodipine combination.

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 intestinal and kidney cells from the transgenic mouse strain MutaMouse and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Amlodipine did not induce gene mutation in bacteria and mouse lymphoma cells; nor did it induce chromosome aberrations in human lymphocytes or Chinese hamster V79 fibroblast *(in vitro)* and in mouse bone marrow cells *(in vivo)*.

Carcinogenicity

There are no carcinogenicity studies with the olmesartan medoxomil/ amlodipine combination.

Olmesartan was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. 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 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan. Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m^2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about two and a half times the MRHD (calculations based on a 60 kg patient).

6   PHARMACEUTICAL PARTICULARS

6.1   LIST OF EXCIPIENTS

Microcrystalline cellulose, colloidal anhydrous silica, pregelatinised maize starch, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, macrogol 3350, titanium

dioxide, purified talc, iron oxide yellow (SEVIKAR 20/10, SEVIKAR 40/5, SEVIKAR 40/10), iron oxide red (SEVIKAR 20/10, SEVIKAR 40/10), and iron oxide black (SEVIKAR 20/10).

6.2   INCOMPATIBILITIES

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

6.3   SHELF LIFE

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

6.4   SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5   NATURE AND CONTENTS OF CONTAINER

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

Not all pack sizes may be available.

6.6   SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7   PHYSICOCHEMICAL PROPERTIES

Olmesartan medoxomil is chemically described 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. The empirical formula is $C_{29}H_{30}N_6O_6$ and its molecular weight is 558.59.

Amlodipine besilate is a racemic mixture and is chemically described as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5- pyridinedicarboxylate benzene sulphonate. The empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1.

Chemical structure

Olmesartan medoxomil has the following structural formula:
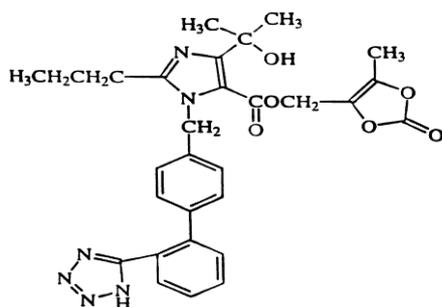
Amlodipine besilate has the following structural formula:
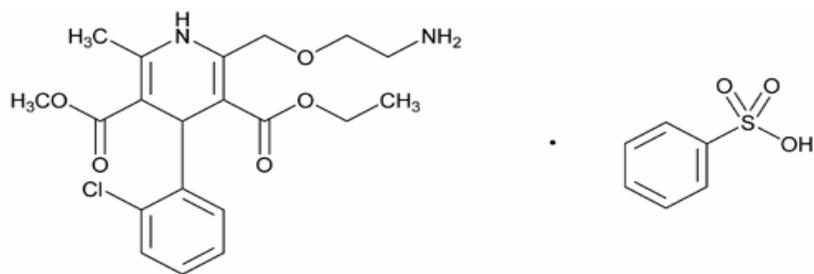
CAS number

The CAS Registry Number is 144689-63-4 (olmesartan medoxomil); 111470-99-6 (amlodipine besilate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

10 May 2010

10 DATE OF REVISION

12 January 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Amend Sponsor Details due to transfer of sponsorship

® Registered Trademark of Daiichi Sankyo Company Ltd

Version 11.0 CCDS ref v8.0