Attachment 1: Product information for AusPAR Sevikar HCT; Olmesartan medoxomil, Amlodipine (as besilate) and Hydrochlorothiazide; Merck Sharp & Dohme Australia Pty Ltd PM-2012-01550-3-3 Date of Finalisation 18 November 2013. This Product Information was approved at the time this AusPAR was published.

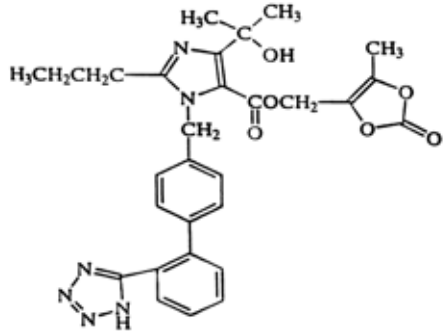
PRODUCT INFORMATION

SEVIKAR® HCT Film coated tablets

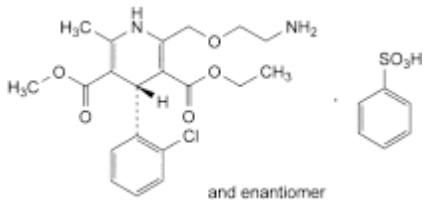
(olmesartan medoxomil/amlodipine (as besilate) and hydrochlorothiazide)
SEVIKAR HCT 20/5/12.5
SEVIKAR HCT 40/5/12.5
SEVIKAR HCT 40/5/25
SEVIKAR HCT 40/10/12.5
SEVIKAR HCT 40/10/25

NAME OF THE MEDICINE

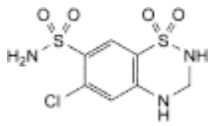
Olmesartan medoxomil is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2 '-(1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl] -1*H*-imidazole-5-carboxylate. The empirical formula is $C_{29}H_{30}N_6O_6$ and its molecular weight is 558.6. Its CAS number is 144689-63-4. Its structural formula is:



Amlodipine besilate is a racemic mixture and is chemically described as 3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate. The empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1. The CAS number is 111470-99-6 and its structural formula is:



Hydrochlorothiazide 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 its molecular weight is 297.7. Its CAS no. is 58-93-5. The structural formula is:



DESCRIPTION

Olmesartan medoxomil is a white or almost white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol (96 per cent), practically insoluble in heptane. The pH of a solution (2% w/v) of olmesartan medoxomil in water is 5.6. The dissociation constant (pKa) is 4.3. The partition coefficient Log P is 1.0 at pH 7.0.

Amlodipine besilate is a white or almost white powder, slightly soluble in water and freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol. The pH of solution (1.0% w/v) of amlodipine besilate is in the pH range of 5.0-7.0. The dissociation constant (pKa) is 8.6.

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

Excipients: microcrystalline cellulose, colloidal anhydrous silica, pregelatinized maize starch, croscarmellose sodium, and magnesium stearate. The colour coating contains polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, and iron oxides.
SEVIKAR HCT 20/5/12.5 mg tablet: OPADRY II complete film coating system 85F24118 PINK.
SEVIKAR HCT 40/5/12.5 mg tablet and SEVIKAR HCT 40/5/25 mg tablet: OPADRY II complete film coating system 85F32331 YELLOW.
SEVIKAR HCT 40/10/12.5 mg tablet and SEVIKAR HCT 40/10/25 mg tablet: OPADRY II complete film coating system 85F25437 PINK.

PHARMACOLOGY

Pharmacodynamic properties

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

The olmesartan medoxomil component of SEVIKAR HCT blocks the vasoconstrictor effects of angiotensin II and the amlodipine component of SEVIKAR HCT inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The hydrochlorothiazide component of SEVIKAR HCT affects the renal tubular mechanisms of electrolyte reabsorption increasing the excretion of sodium and chloride.

<u>Olmesartan medoxomil</u>

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.

Hydrochlorothiazide

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

The effectiveness of olmesartan medoxomil/ hydrochlorothiazide combination therapy was maintained over long-term (1-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension. The effects of fixed dose combination of olmesartan medoxomil/ hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

Pharmacokinetics

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

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

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

The terminal elimination half-life of olmesartan varied between 10 and 15 hours. 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.

<u>Amlodipine</u>
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
Amlodipine is extensively metabolised by the liver to inactive metabolites. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Excretion
10% of the parent compound and 60% of metabolites are excreted in the urine.

Hydrochlorothiazide
Absorption
Following oral administration of olmesartan medoxomil, amlodipine and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing.

Distribution
Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83–1.14 L/kg.

Metabolism
Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged drug in urine.

Excretion
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 hydrochlorothiazide is 10-15 hours.

Pharmacokinetics in special populations
Elderly
The pharmacokinetic properties of SEVIKAR HCT 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 HCT 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 gender had no effect on the clearance of olmesartan medoxomil and amlodipine. Female patients had approximately 20% smaller clearances of hydrochlorothiazide than male patients.

Olmesartan medoxomil
Minor differences were observed in the pharmacokinetics of olmesartan medoxomil in women compared to men. AUC and Cmax 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%.

CLINICAL TRIALS

SEVIKAR HCT

The antihypertensive efficacy of SEVIKAR HCT was studied in a double-blind, active-controlled study [CS8635-A-U301] in hypertensive patients. A total of 2492 patients with hypertension (mean baseline blood pressure 169/101 mmHg) received olmesartan medoxomil/ amlodipine/ hydrochlorothiazide 40/10/25 mg (627 patients), olmesartan medoxomil/amlodipine 40/10 mg (628 patients), olmesartan medoxomil/hydrochlorothiazide 40/25 mg (637 patients), or amlodipine/hydrochlorothiazide 10/25 mg (600 patients).

Each subject was randomised to one of the three dual therapy combinations for two to four weeks. Patients were then randomised to continue on the dual therapy they were receiving or to receive triple therapy. A total of 53% of patients were male, 19% were 65 years or older, 67% were white, 30% were black, and 15% were diabetic.

After 8 weeks of treatment, the triple combination therapy produced greater reductions in both systolic and diastolic blood pressures ($p< 0.0001$) compared to each of the 3 dual combination therapies.

The seated blood pressure reductions attributable to the addition of a single high-dose drug to each high-dose dual drug combination are shown in Table 1.

Table 1 Additional blood pressure reductions on high-dose SEVIKAR HCT compared to high doses of dual combination drugs

Start on	Adding	BP reduction*
Olmesartan medoxomil 40 / amlodipine 10 mg	HCT 25 mg	8.4/4.5 mmHg
Olmesartan medoxomil 40 / HCT 25 mg	Amlodipine 10 mg	7.6/5.4. mmHg
Amlodipine 10 / HCT 25 mg	Olmesartan medoxomil 40 mg	8.1/5.4 mmHg

* all highly statistically significant.

There were no apparent differences in terms of seated diastolic blood pressure (SeDBP) or seated systolic blood pressure (SeSBP) reductions in black and non-black patients treated with SEVIKAR HCT.

There were no apparent differences in terms of SeDBP or SeSBP reductions in diabetic and non-diabetic patients treated with SEVIKAR HCT.

A total of 440 patients participated in the ambulatory blood pressure monitoring portion of the study. Over the 24-hour period, there was a greater reduction in diastolic and systolic ambulatory blood pressure for olmesartan medoxomil/amlodipine/hydrochlorothiazide 40/10/25 mg compared to each of the dual combination therapies (see Figure 1 and Figure 2).

Figure 1: Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Hour

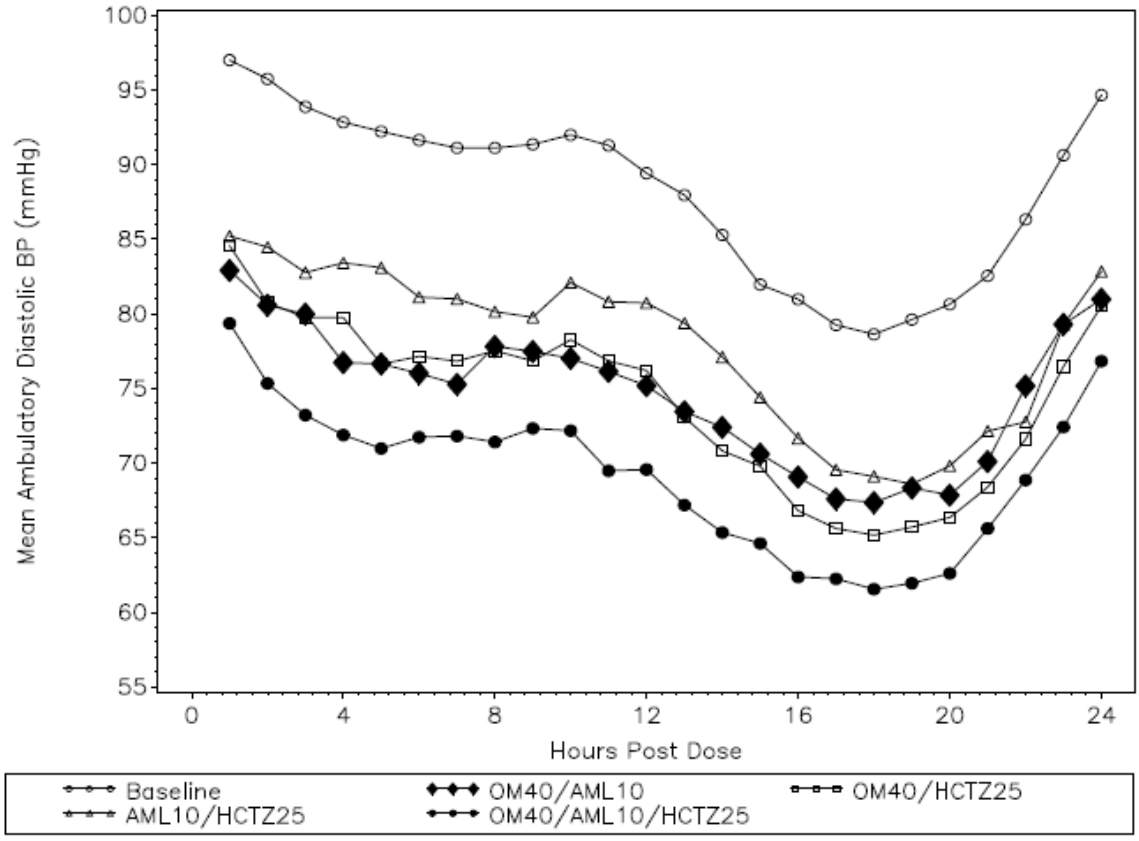
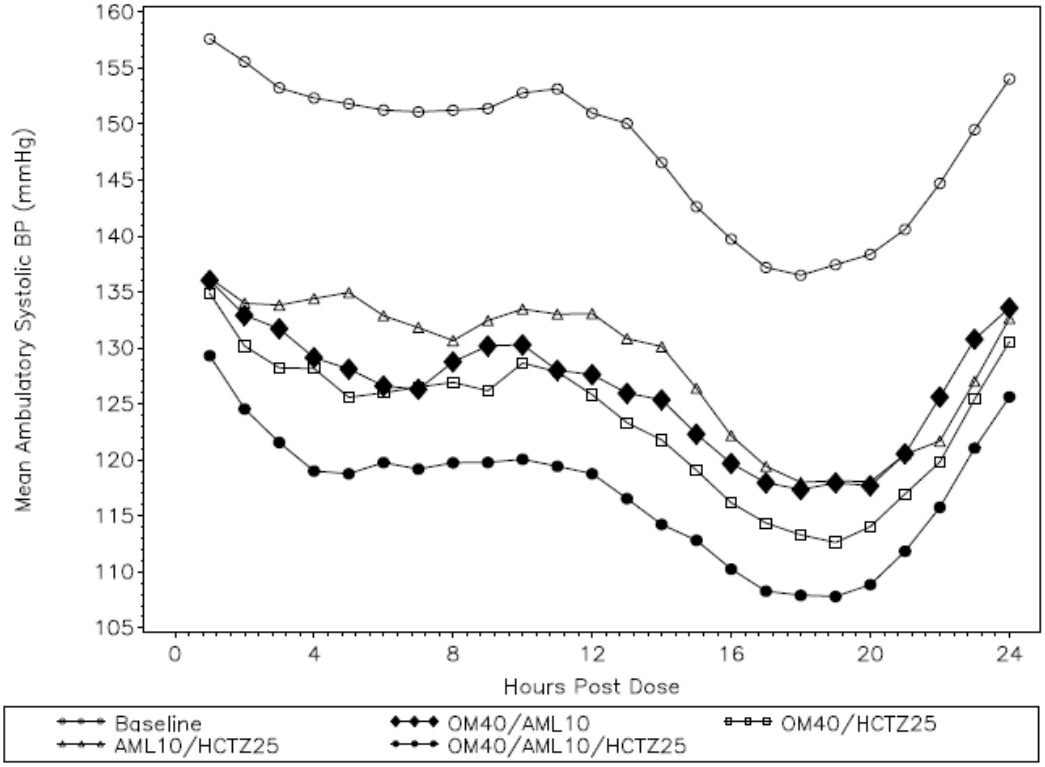


Figure 2: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour



In a second double-blind, randomised, parallel-group study [CS8635-A-E302] in 2690 patients (99.9% Caucasian patients), treatment with SEVIKAR HCT (20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, 40 mg/10 mg/25 mg) resulted in significantly greater reductions in diastolic and systolic blood pressure compared to the corresponding dual combinations, olmesartan medoxomil 20 mg plus amlodipine 5 mg, olmesartan medoxomil 40 mg plus 5 mg amlodipine and olmesartan medoxomil 40 mg plus 10 mg amlodipine, respectively, after 10 weeks of treatment.

The additional blood pressure lowering effect from SEVIKAR HCT compared to the corresponding dual combinations was between -1.3 and -1.9 mmHg for seated diastolic and between -2.7 and -4.9 mmHg for seated systolic blood pressure.

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) at week 10 ranged from 42.7% to 49.6% for the dual combination treatment groups compared to 52.4% to 58.8% for SEVIKAR HCT.

In a randomised, double-blind, add-on study [CS8635-A-E303] in 808 patients (99.9 % Caucasian patients) not adequately controlled after 8-weeks therapy with olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination, treatment with SEVIKAR HCT resulted in numerically additional seated blood pressure reduction of -1.8/-1.0 mmHg when treated with SEVIKAR HCT 40 mg/10 mg/12.5 mg and a statistically significant additional seated blood pressure reduction of -3.6/-2.8 mmHg when treated with SEVIKAR HCT 40

mg/10 mg/25 mg compared to the olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination.

Treatment with SEVIKAR HCT 40 mg/10 mg/25 mg triple-combination therapy resulted in a statistically significantly greater percentage of subjects reaching their blood pressure goal compared to olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination therapy (41.3% vs. 24.2%); while the treatment with SEVIKAR HCT 40 mg/10 mg/12.5 mg triple-combination therapy resulted in a numerically greater percentage of subjects reaching their blood pressure goal compared to olmesartan medoxomil 40 mg plus amlodipine 10 mg dual-combination therapy (29.5% vs. 24.2%) in subjects not adequately controlled on dual-combination therapy.

The antihypertensive effect of SEVIKAR HCT was similar irrespective of age and gender, and was similar in patients with and without diabetes although the number of patients aged ^{3} 75 years and the number of patients with diabetes were limited.

The blood pressure lowering effects of lower dose strengths of SEVIKAR HCT (olmesartan medoxomil/amlodipine/hydrochlorothiazide 20/5/12.5 mg, 40/5/12.5 mg, 40/10/12.5 mg, and 40/5/25 mg) have not been studied.

All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of SEVIKAR HCT (olmesartan medoxomil/amlodipine/hydrochlorothiazide) is expected to be 20/5/12.5 mg < 40/5/12.5 mg < (40/10/12.5 mg ≈ 40/5/25 mg) < 40/10/25 mg.

There are no trials of SEVIKAR HCT demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

INDICATIONS

SEVIKAR HCT is indicated for the treatment of hypertension, either as replacement for olmesartan medoxomil, amlodipine and hydrochlorothiazide being already taken as separate tablets or as add-on therapy where a patient's blood pressure is not controlled on a dual combination (see DOSAGE AND ADMINISTRATION).
This fixed dose combination **is not** indicated for initial therapy.

CONTRAINDICATIONS

SEVIKAR HCT is contraindicated in:

- Patients who are hypersensitive to any component of the tablet, to dihydropyridines, to thiazides or to other sulphonide-derived drugs.
- 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).

Due to the component amlodipine, SEVIKAR HCT is also contraindicated in:
- Cardiogenic shock
- Acute myocardial infarction (within the first 4 weeks)
- Unstable angina pectoris

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 SEVIKAR HCT.

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, azotemia, oliguria, or rarely, 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
When SEVIKAR HCT is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of SEVIKAR HCT is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see CONTRAINDICATIONS).

<u>Amlodipine</u>
Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Hydrochlorothiazide

Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. There is no experience of the administration of SEVIKAR HCT in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance < 12 mL/min).

Impaired renal function and/or Azotaemia: When creatinine clearance falls below 30 mL/min thiazide diuretics are ineffective. Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

An adverse event of impaired renal function was reported in 2.1% of subjects receiving SEVIKAR HCT compared to 0.2% to 1.3% of subjects receiving dual combination therapy.

Hepatic impairment

Since amlodipine is extensively metabolised by the liver, exposure to amlodipine is increased in patients with hepatic impairment. 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.

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

Care should be taken when SEVIKAR HCT is administered in patients with mild to moderate impaired hepatic function or progressive liver disease. Careful monitoring should be performed. A lower starting dose may be required (see DOSAGE AND ADMINISTRATION).

Use of SEVIKAR HCT in patients with severe hepatic impairment, (Child-Pugh score 10-15), cholestasis and biliary obstruction is contraindicated (see CONTRAINDICATIONS).

Electrolyte imbalance

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

Careful check should be kept for signs of fluid and electrolye imbalance. Thiazides, including HCT, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia hypochloraemic alkalosis and hypomagnesaemia). It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids.Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see ADVERSE EFFECTS).

Hypokalaemia may develop with hydrochlorothiazide as with any other potent diuretic, especially with brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability). The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see INTERACTIONS WITH OTHER MEDICINES).

Conversely, due to antagonism at the angiotensin-II receptors (AT_1) and ACE inhibitors, hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with SEVIKAR HCT (see INTERACTIONS WITH OTHER MEDICINES) and with frequent monitoring of potassium levels.

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

Diuretic induced hyponatraemia is usually mild and asymptomatic. In a few patients hyponatraemia may become severe and symptomatic. Such patients require immediate attention and appropriate treatment.

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

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

Dilutional hyponatraemia may occur in oedematous patients in hot weather.

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; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. SEVIKAR HCT should be immediately discontinued in patients who develop angioedema, and SEVIKAR HCT should not be re-administered.

Metabolic and endocrine effects

Hyperuricaemia may occur or gout may be precipitated in certain patients receiving thiazide therapy. Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy
Due to the amlodipine component of SEVIKAR HCT, as with all vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy. Amlodipine should be used with caution in the presence of a fixed left ventricular outflow obstruction (aortic stenosis).

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 HCT is not recommended in such patients.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with SEVIKAR HCT, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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 HCT 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. 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 INTERACTIONS WITH OTHER MEDICINES).

Lithium should not be given with thiazide diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulphonamide, 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 sulphonamide or penicillin allergy.

Systemic Lupus Erythematosus

Thiazide diuretics (e.g. hydrochlorothiazide) have been reported to cause exacerbation or activation of systemic lupus erythematosus.

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. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Effects on fertility

The effects of olmesartan, amlodipine and hydrochlorothiazide in combination on fertility have not been investigated.

Olmesartan medoxomil
Fertility of rats was unaffected by administration of olmesartan at dose levels as high as 1000 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.

Amlodipine
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 amlodipine up to 10 mg/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

Hydrochlorothiazide
No animal fertility studies are available for hydrochlorothiazide.

Use in pregnancy (Category D)
SEVIKAR HCT can cause foetal harm when administered to a pregnant woman. As a precaution, SEVIKAR HCT 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 HCT must be discontinued as soon as possible. There is no experience of the use of SEVIKAR HCT in pregnant women.

If SEVIKAR HCT is used during pregnancy, or if the patient becomes pregnant while taking SEVIKAR HCT, the patient should be apprised of the potential hazard to a foetus. Should exposure to SEVIKAR HCT 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

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 SEVIKAR HCT 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, SEVIKAR HCT 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.

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

Category C. 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.

Safety of amlodipine in human pregnancy or lactation has not been established.

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.

Thiazide diuretics

Category C. Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated and exposes mother and foetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia.

Thiazides cross the placental barrier and appear in cord blood.

Use of thiazides when pregnancy is present or suspected requires that the benefits of the drug be weighed against possible hazards to the foetus. These hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occurred in the adult.

Use in lactation

Olmesartan medoxomil and Amlodipine besilate

It is not known whether the olmesartan medoxomil or amlodipine components of SEVIKAR HCT 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.

In the absence of the above information, breast-feeding should be discontinued during the treatment with SEVIKAR HCT.

Thiazides appear in human milk. If use of the drug is deemed essential, the patient should stop nursing.

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

Olmesartan medoxomil
Safety and effectiveness have not been established in children.

Amlodipine
Safety and effectiveness have not been established in children.

Use in the elderly
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 (refer to DOSAGE AND ADMINISTRATION).

Blood pressure should be frequently monitored in the elderly.
There are limited data available with this triple combination in those aged ≥ 75 years.

Olmesartan medoxomil
Of the total number of hypertensive patients receiving OLMETEC 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.

Amlodipine
In elderly patients (≥ 65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse events in elderly patients was approximately 6% higher than that of younger population (< 65 years). Adverse events include oedema, muscle cramps and dizziness.

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

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 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). On balance, the weight-of-evidence indicates that olmesartan medoxomil does not pose a genotoxic risk at clinically relevant doses.

Amlopidine
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*).

Hydrochlorothiazide
Hydrochlorothiazide 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 hydrochlorothiazide concentrations of 43-1,200 mg/mL.

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

Olmesartan medoxomil
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.

Amlopidine
The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Rats and mice treated with amlodipine maleate in the diet for up to 2 years, at concentrations calculated to provide daily dosage levels of amlodipine 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of a carcinogenic effect of the drug. The highest dose was, on a mg/m^2 basis, similar to the MRHD of amlodipine 10 mg/day for both rodent species.

Hydrochlorothiazide
Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). There was equivocal

evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide alone at approximately 600 mg/kg/day.

Effects on laboratory tests

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

Amlodipine
In post-marketing experience, hepatic enzyme elevations have been reported.

Hydrochlorothiazide
Increase in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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.

INTERACTIONS WITH OTHER MEDICINES

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

Olmesartan medoxomil
Medicines, 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.

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

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. Olmesartan is not

metabolised by cytochrome P450 and has no effect on P450 enzymes. Therefore, interactions with drugs that inhibit, induce or are metabolised by those enzymes are not expected.

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.

Cyclosporin
The pharmacokinetics of cyclosporin were not altered when cyclosporin was co-administered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.

Hydrochlorothiazide
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 hydrochlorothiazide.

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

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

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.

Medicinal products affecting potassium levels
The potassium-depleting effect of hydrochlorothiazide 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 SEVIKAR HCT, monitoring of potassium plasma levels is advised.

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 SEVIKAR HCT tablets and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Other drugs

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 hydrochlorothiazide 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 SEVIKAR HCT 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.

Lithium should not be given with thiazide diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when SEVIKAR HCT 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).

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.

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

ADVERSE EFFECTS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

SEVIKAR HCT

In the controlled trials of SEVIKAR HCT, patients were randomised to (doses in mg): SEVIKAR HCT (olmesartan medoxomil/amlodipine/hydrochlorothiazide) 20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5 or 40/10/25, olmesartan medoxomil/amlodipine 20/5, 40/5 or 40/10, olmesartan medoxomil/hydrochlorothiazide 40/25, or amlodipine/hydrochlorothiazide 10/25. The duration of exposure to any olmesartan medoxomil/amlodipine/ hydrochlorothiazide triple-combination therapy was ≥26 weeks for 1914 subjects, ≥48 weeks for 331 subjects, and ≥52 weeks for 7 subjects.

The frequency of adverse reactions was similar between men and women, patients < 65 years of age and patients ≥ 65 years of age, and patients with and without diabetes.

Discontinuations due to adverse events were comparable across all triple combination treatment groups, and to groups of subjects treated with dual combinations. The number of discontinuations due to adverse events, and the most frequent adverse events that occurred in at least 2% of patients treated with SEVIKAR HCT are presented in the table below:

Table 2: Discontinuations and adverse events with ≥ 2% incidence in patients treated with SEVIKAR HCT

n (%)	OM20/ AML5 (N = 337)	OM40/ AML5 (N = 343)	OM40/ AML10 (N = 3168)	OM40/ HCT25 (N = 637)	AML10/ HCT25 (N = 600)	OM20/ AML5 HCT12.5 (N = 2556)	OM40/ AML5 HCT12.5 (N = 2971)	OM40/ AML5/ HCT25 (N = 1138)	OM40/ AML10/ HCT12.5 (N = 1776)	OM40/ AML10/ HCT25 (N = 1955)
Discontinuations	5 (1.5)	9 (2.6)	93 (2.9)	50 (7.8)	43 (7.2)	19 (0.7)	70 (2.4)	17 (1.5)	33 (1.9)	91 (4.7)
Averse Events										
Nasopharyngitis	7 (2.1)	11 (3.2)	34 (1.1)	21 (3.3)	16 (2.7)	41 (1.6)	70 (2.4)	24 (2.1)	30 (1.7)	58 (3.0)
Upper respiratory tract infrection	0 (0.0)	1 (0.3)	40 (1.3)	18 (2.8)	15 (2.5)	5 (0.2)	73 (2.5)	12 (1.1)	22 (1.2)	55 (2.8)
Urinary tract infection	1 (0.3)	0 (0.0)	9 (0.3)	7 (1.1)	9 (1.5)	5 (0.2)	60 (2.0)	15 (1.3)	8 (0.5)	37 (1.9)
Dizziness	5 (1.5)	5 (1.5)	43 (1.4)	71 (11.1)	23 (3.8)	22 (0.9)	103 (3.5)	33 (2.9)	34 (1.9)	112 (5.7)
Headache	16 (4.7)	8 (2.3)	75 (2.4)	43 (6.8)	37 (6.2)	44 (1.7)	68 (2.3)	31 (2.7)	42 (2.4)	87 (4.5)
Peripheral oedema	11 (3.3)	17 (5.0)	205 (6.5)	8 (1.3)	59 (9.8)	31 (1.2)	57 (1.9)	17 (1.5)	72 (4.1)	125 (6.4)
Fatigue	1 (0.3)	0 (0.0)	45 (1.4)	33 (5.2)	36 (6.0)	2 (0.1)	45 (1.5)	13 (1.1)	6 (0.3)	43 (2.2)

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

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, syncope
Psychiatric disorders:	Uncommon: Libido decreased
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

Additional information on the individual components
Adverse events previously reported with one of the individual components may be potential adverse events with SEVIKAR HCT, even if not observed in clinical trials with this product.

Olmesartan medoxomil
Olmesartan medoxomil has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 treated for at least 1 year. Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse events similar to that seen with placebo. Events were generally mild, transient, and without 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., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 32/1179) 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 in olmesartan medoxomil treated patients vs. placebo was dizziness (3% vs 1%).

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%.

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
Metabolic and nutritional:	Common: Increased creatine phosphokinase, hyperglycaemia, hypertriglyceridaemia, hyperuricaemia; Rare: Hyperkalaemia
Liver and biliary:	Common: Liver enzyme elevations

Post-marketing experience

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

Body as whole:	Angioedema; asthenic conditions, such as asthenia, fatigue, lethargy, malaise, anaphylactic reactions
Gastrointestinal:	Abdominal pain; nausea; vomiting
Liver and biliary system disorders:	Hepatic enzymes increased
Metabolic and nutritional disorders:	Hyperkalaemia
Musculoskeletal:	Rhabdomyolysis; myalgia
Nervous systems disorders:	Headache
Respiratory, thoracic and mediastinal disorders:	Cough
Skin and appendages:	Alopecia; rash; pruritus; urticaria
Urogenital system:	Acute renal failure; increased blood creatinine levels

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%). 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.

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

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:

	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, peripheral ischaemia, syncope, tachycardia, postural dizziness, postural hypotension, angioedema
Central and Peripheral Nervous System:	Hypoesthesia, paraesthesia, tremor, vertigo, peripheral neuropathy
Endocrine:	Gynaecomastia
Gastrointestinal:	Anorexia, 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
Haemopoietic:	Purpura, leucopenia, thrombocytopenia
Metabolic and Nutritional:	Thirst, hyperglycaemia
Musculoskeletal System:	Arthralgia, arthrosis, muscle cramps, myalgia
Psychiatric:	Sexual dysfunction (male and female), insomnia,

	nervousness, depression, abnormal dreams, anxiety, depersonalisation, mood changes
Respiratory System:	Dyspnoea, epistaxis
Skin and Appendages:	Alopecia, pruritus, rash, rash erythematous, rash maculopapular, vasculitis
Special Senses:	Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus
Urinary System:	Micturition frequency, micturition disorder, nocturia

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: cardiac failure, pulse irregularity, extrasystoles, skin discolouration, 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.

<u>Hydrochlorothiazide</u>
Hydrochlorothiazide may cause or exacerbate volume depletion, which may lead to electrolyte imbalance (see PRECAUTIONS).

Adverse events reported with the use of Hydrochlorothiazide alone include:

Blood and lymphatic system:	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression.
Cardiovascular:	Cardiac arrhythmias
Central nervous system:	Restlessness, light-headedness, vertigo, paraesthesiae
Eye:	Xanthopsia, transient blurred vision
Gastrointestinal system:	Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation, sialadenitis, pancreatitis
General:	Fever
Hepatobiliary:	Jaundice (intrahepatic cholestatic jaundice)
Musculoskeletal:	Muscle spasm, weakness
Psychiatric:	Sleep disturbances, depression
Respiratory system:	Respiratory distress (including pneumonitis and pulmonary oedema*)*

Skin and appendages:	Photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus, erythematosus, urticaria, necrotising angiitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, toxic epidermal necrolysis
Urinary system:	Renal failure, renal dysfunction, interstitial nephritis
Vascular:	Postural hypotension
Laboratory parameters:	Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides.

DOSAGE AND ADMINISTRATION

SEVIKAR HCT is registered in five strengths:

1) SEVIKAR HCT 20/5/12.5 (olmesartan medoxomil 20 mg, amlodipine as besilate 5 mg and hydrochlorothiazide 12.5 mg);
2) SEVIKAR HCT 40/5/12.5 (olmesartan medoxomil 40 mg and amlodipine as besilate 5 mg and hydrochlorothiazide 12.5 mg);
3) SEVIKAR HCT 40/5/25 (olmesartan medoxomil 40 mg and amlodipine as besilate 5 mg and hydrochlorothiazide 25 mg);
4) SEVIKAR HCT 40/10/12.5 (olmesartan medoxomil 40 mg, amlodipine as besilate 10 mg and hydrochlorothiazide 12.5 mg);
5) SEVIKAR HCT 40/10/25 (olmesartan medoxomil 40 mg, amlodipine as besilate 10 mg and hydrochlorothiazide 25 mg).

(See PRESENTATION AND STORAGE CONDITIONS for marketed strengths).

The recommended dosage of SEVIKAR HCT is one tablet daily, with or without food. Treatment should not be initiated with this combination. Treatment should be taken at the same time each day. The tablet should not be chewed. The maximum dose is 40/10/25 mg once daily.

Replacement therapy

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

Add-on therapy

For patients whose blood pressure is not adequately controlled on olmesartan and amlodipine or olmesartan and hydrochlorothiazide or amlodipine and hydrochlorothiazide therapy, they may be switched to combination therapy with SEVIKAR HCT. Titration of the dosage is recommended. For patients whose blood pressure is not adequately controlled on SEVIKAR HCT 20/5/12.5, then titration to SEVIKAR HCT 40/5/12.5 is recommended. Subsequently, if the patient's blood pressure is not adequately controlled on SEVIKAR HCT 40/5/12.5, then titration to the maximum SEVIKAR HCT 40/10/25 is recommended.

Dosage may be increased after 2 weeks to a maximum dose of 40/10/25 mg once daily, usually by increasing one component at a time but any component can be raised to achieve more rapid control.

Maximum antihypertensive effects are attained within 2 weeks after a change in dose.

Renal insufficiency
No adjustment of the recommended dose is required for patients with mild (creatinine clearance of 50-80 mL/min) to moderate (creatinine clearance of 30 - < 50 mL/min) impairment of renal function. When SEVIKAR HCT is used in such patients, periodic monitoring of renal function is advised (see PRECAUTIONS).

The use of SEVIKAR HCT in patients with severe renal impairment (creatinine clearance < 30 mL/min) is contraindicated (see CONDRAINDICATIONS).

Hepatic insufficiency
SEVIKAR HCT should be used with caution in 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). SEVIKAR HCT 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.

In patients with hepatic insufficiency, the starting dose of amlodipine is usually 2.5 mg and this dose is not available in the triple combination.

Intravascular volume depletion
For patients with possible depletion of intravascular volume, particularly those with impaired renal function, SEVIKAR HCT should be administered under close medical supervision.
If a patient becomes volume depleted whilst taking SEVIKAR HCT, blood pressure and renal function should be closely monitored until the situation resolves.

Elderly
No adjustment of the recommended dose is generally required for elderly patients. In the small, frail or elderly, the starting dose of amlodipine is 2.5 mg and this dose is not available in the triple combination.

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of SEVIKAR HCT 40 mg/10 mg/25 mg per day.

Very limited data are available on the use of SEVIKAR HCT in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

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

OVERDOSAGE

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

Symptoms

There is no experience of overdose with SEVIKAR HCT. 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.

Overdosage with hydrochlorothiazide 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.

Treatment

If intake is recent, gastric lavage or induction of emesis may be considered. 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 HCT 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.
No information is available regarding the dialysability of olmesartan or hydrochlorothiazide.
For further advice on the management of an overdose contact the Poisons Information Centre.

PRESENTATION AND STORAGE CONDITIONS

SEVIKAR HCT 20/5/12.5 mg contains 20 mg olmesartan medoxomil, 5 mg amlodipine as besilate and 12.5 mg hydrochlorothiazide. It is a round film-coated tablet, approximately 8 mm in diameter, orange white in colour with C51 debossed on one side.

SEVIKAR HCT 40/5/12.5 mg contains 40 mg of olmesartan medoxomil, 5 mg amlodipine as besilate and 12.5 mg hydrochlorothiazide. It is a round film-coated tablet, approximately 9.5 mm in diameter, light yellow in colour with C53 debossed on one side.

SEVIKAR HCT 40/5/25 mg contains 40 mg of olmesartan medoxomil, 5 mg amlodipine as besilate and 25 mg hydrochlorothiazide. It is an oval film-coated tablet, approximately 15x7 mm, light yellow in colour with C54 debossed on one side.

SEVIKAR HCT 40/10/12.5 mg contains 40 mg of olmesartan medoxomil, 10 mg amlodipine as besilate and 12.5 mg hydrochlorothiazide. It is a round film-coated tablet, approximately 9.5 mm in diameter, greyish red in colour with C55 debossed on one side.

SEVIKAR HCT 40/10/25 mg contains 40 mg of olmesartan medoxomil, 10 mg amlodipine as besilate and 25 mg hydrochlorothiazide. It is an oval film-coated tablet, approximately 15x7 mm, greyish red in colour with C57 debossed on one side.

SEVIKAR HCT 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
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Australia

POISON SCHEDULE OF THE MEDICINE
Prescription only medicine (Schedule 4)

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
20 September 2013