Australian Government

Department of Health and Ageing

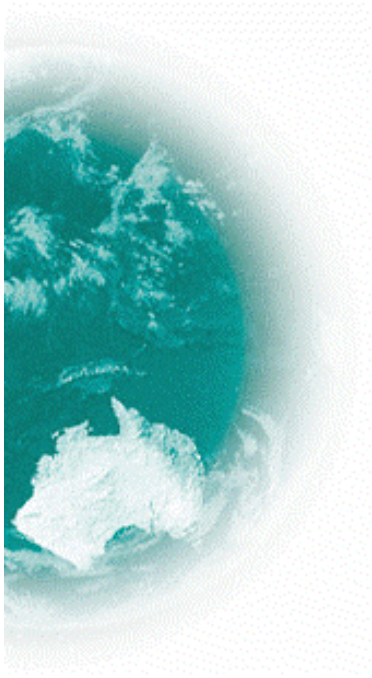
Therapeutic Goods Administration

Australian Public Assessment Report
for
Olmesartan medoxomil and amlodipine besylate

Proprietary Product Name: Sevikar

Submission No: PM-2008-03320-3-3

Sponsor: Schering-Plough Pty Ltd



September 2010

Contents

I. Introduction to Product Submission

Product Submission Details

Type of Submission	New Fixed Dose Combination
Decision:	Approved
Date of Decision:	10 May 2010
Active ingredient(s):	Olmesartan medoxomil Amlodipine besylate
Product Name(s):	Sevikar
Sponsor's Name and Address:	Schering-Plough Pty Ltd Level 4, 66 Waterloo Road North Ryde NSW 2113
Dose form(s):	Tablet
Strength(s):	20 mg olmesartan medoxomil/5 mg amlodipine (as besylate), 20 mg olmesartan medoxomil/10 mg amlodipine (as besylate), 40 mg olmesartan medoxomil/5 mg amlodipine (as besylate), and 40 mg olmesartan medoxomil/10 mg amlodipine (as besylate)
Container:	PA/Al/PVC\\Al Blister packs
Pack size(s):	Packs of 10 and 30
Approved Therapeutic use:	Sevikar is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.
Route(s) of administration:	Oral
Dosage:	One tablet daily
ARTG Number (s)	157562, 157563, 157564, 157565

Product Background

Olmesartan medoxomil (OM) is a prodrug which is rapidly converted to the pharmacologically active metabolite olmesartan by esterases in the gut mucosa and portal blood during absorption from the gastrointestinal tract. OM is a potent and selective angiotensin type 1 (AT1) receptor blocker (ARB). In Australia, the approved indication for OM is the treatment of hypertension.

Amlodipine (AML) (present in the OM/AML fixed-dose combination as the besylate salt) is a calcium channel blocker (CCB) of the dihydropyridine type and is a well-established antihypertensive agent approved in Australia. AML inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mode of action of AML differs from, and is complementary to, that of olmesartan. AML is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and hence a reduction in blood pressure (BP). The usual initial dosage of AML in hypertension is 2.5 - 5 mg once daily (od) which may be increased to a maximum dose of 10 mg od, depending on the individual patient's response.

Concomitant use of an ARB and a CCB is a rational choice of combination antihypertensive therapy. The two classes of agent have different modes of action and provide independent BP lowering effects. Dihydropyridine CCBs activate the sympathetic nervous system and renin-angiotensin-aldosterone axis, effects which are buffered by co-administration of a drug which

inhibits the renin-angiotensin system. In additions, CCBs are natriuretic and induce a state of negative sodium balance, which further reinforces the antihypertensive effects of drugs acting on the renin-angiotensin system. Furthermore, peripheral oedema is one of the most common adverse effects of dihydropyridine CCBs and probably results from vasodilatation and reduction in pre-capillary resistance. This effect can be ameliorated during concomitant use with ARBs, which lower post-capillary resistance and hence tend to normalise intracapillary pressure and reduce fluid exudation. The European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines on the clinical management of hypertension published in 2003, and updated in 2007, recognise ARB/CCB combination treatment as an effective and well-tolerated therapeutic option (ESH/ESC Guidelines Committee, 2007).

It is proposed that Sevikar be indicated for the treatment of hypertension. The indication proposed is as follows:

initial therapy in patients likely to need multiple antihypertensive agents to achieve their target BP goal, and

treatment of hypertension in patients whose blood pressure is not adequately controlled on either angiotensin receptor blocker, angiotensin converting enzyme (ACE) inhibitor or dihydropyridine calcium channel antagonist monotherapies.

Regulatory Status

Olmetec tablets containing 10, 20 and 40 mg of olmesartan medoxomil were approved for registration by Pfizer Australia Pty Ltd in September 2005 with the indication, 'treatment of hypertension' (AUST R 102134, 102138 and 102139). The sponsorship of these products was then transferred to Schering-Plough Pty Limited in February 2007. There are no generics.

Olmetec Plus 20/12.5, 20/25, 40/12.5 and 40/25 fixed dose combination tablets of olmesartan medoxomil with hydrochlorothiazide were registered to Pfizer Australia Pty Ltd in June 2006 (and sponsorship transferred to Schering-Plough Pty Limited in February 2007) with the same indication (AUST R 115738, 115732, 115737 and 115661). However 'treatment should not to be initiated with this fixed dose combination'. There are no generics.

Tablets containing the 2.5, 5 and 10 mg of amlodipine (as the besylate) have been registered for many years (1993) for the treatment of hypertension. Pfizer would appear to be the innovator, but there are many generics. Fixed dose combination tablets with valsartan (Novartis) and atorvastatin (as calcium; Pfizer) have been registered.

A similar application to the current Australian submission has been submitted and approved in the USA and the European Union (EU) (by the Mutual Recognition procedure).

In the USA the olmesartan medoxomil/amlodipine combination is marketed as Azor. It was approved on 27 November 2006 for use in the treatment of hypertension; however it was not approved for use as initial therapy. Subsequently further data were submitted in the USA, and in May 2009 the FDA approved Azor for use as initial therapy for treatment of hypertension.

The dataset submitted in Australia includes data submitted in the original applications in the USA and EU, as well as further additional efficacy and safety data that were submitted in the USA in the application for first-line therapy. The Australian dataset also includes a section in the sponsor's Clinical Overview that outlines a justification for switching of patients on any angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or dihydropyridine calcium channel blocker (CCB) to Sevikar.

In the US Azor is indicated as follows:

AZOR is indicated for the treatment of hypertension, alone or with other antihypertensive agents.

AZOR may also be used as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

The approved EU indication for Sevikar is:

Treatment of essential hypertension.

Sevikar is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy.

Sevikar has also been approved in Switzerland (8 October 2008) with an indication identical to that in the EU and approval has also been granted in Brazil, Korea and Taiwan.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

All details relating to olmesartan medoxomil drug substance are the same as for the registered products. There are no EP, BP or USP monographs for olmesartan medoxomil or any dosage forms containing this drug substance.[1]

There is an EP6.4/BP2010 monograph for amlodipine besilate[2] and a USP32 monograph for amlodipine besylate, but no monographs for finished products containing this drug substance. Two different manufacturers are used for the amlodipine besylate used in the Sevikar products. The material from each is covered by an EDQM Certificate of Suitability (CEP) certifying that the material meets the EP6.4/BP2010 monograph for amlodipine besilate. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution and residual solvents. The sponsor provided data to demonstrate that levels of alkyl besylates (which are genotoxic and can be formed from besylate ions and methanol or iso-propanol used in the manufacture of amlodipine besylate) are orders of magnitude lower than levels that would be of concern.

Drug Product

The tablets are to be manufactured by Daiichi Sankyo Europe GmbH in Germany. The process is a simple dry compression involving milling of olmesartan medoxomil, blending with amlodipine besylate and excipients, lubrication, compression, film-coating and packaging. The company satisfied the evaluator that no alkyl besylates could be formed during the manufacture. The milled olmesartan medoxomil has limits for particle size distribution. These limits were as accepted for the monotherapy tablets. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. No material of animal origin is used.

The cores of the of the 20/5 and 40/10 tablets are direct scales, and those of the other strengths are based on the 40/10 tablet with the different amounts of the drug substances being compensated for with different amounts of microcrystalline cellulose and colloidal anhydrous silica. Although the tablets are all the same shape (round), the tablets are distinguished by colour and markings (and size for the 20/5 tablet). Finally, the strengths are further distinguished by different colour cartons.

The manufacture of the tablets is well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage.

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[1] EP: European Pharmacopoeia, BP: British Pharmacopoeia, USP: United States Pharmacopoeia

[2] Note the Australian Approved Name (AAN) at the time of writing is amlodipine besylate and not amlodipine besilate.

Stability data was provided to support the proposed shelf lives of 3 years when stored below 25ºC in opaque PA/Al/PVC // Al blister packs. The storage conditions 'protect from moisture' and 'protect from light' are not required.

Bioavailability

Clinical Background

The pivotal Phase III efficacy studies were performed with co-administration of single entity olmesartan medoxomil tablets and amlodipine tablets.

- The same 5 mg and 10 mg amlodipine tablets (commercially available innovator product from Italy) were used throughout the efficacy studies and in the bioavailability studies.
- The Australian-registered 10 mg, 20 mg and 40 mg olmesartan medoxomil tablets were used in all of the efficacy studies.

Studies submitted

Eleven bioavailability studies were submitted. All the studies are prefixed with CS8663-A-.

Studies U103, U104, U105, U106, U113 and U114 compared test formulations of the fixed-dose combination tablets against co-administration of the separate entities as their marketed formulations (olmesartan medoxomil 40 mg + Italian commercially available amlodipine 10 mg). As none of these formulations (A, B, C, D or H) were proposed for supply in Australia and other studies were provided comparing the proposed formulation (G), they were not evaluated by the quality evaluator. Thus the results are not reported in this summary.

The test methods used in the other studies to determine levels of olmesartan (the active metabolite of the pro-drug olmesartan medoxomil) and amlodipine in subjects' plasma samples were evaluated and found to give accurate and precise results.

Study U109 (Formulation G)

This was an open-label, single-dose 2-way cross-over study in 28 healthy subjects (13 male, 15 female), with both treatments administered in the morning following an overnight fast.

Table 1: Pharmacokinetic (PK) Results from Study CS8663-A-U109

Parameter	Geometric Mean Ratio (Fixed/Free) and [90% Confidence Intervals]	
	Olmesartan	Amlodipine
AUC_{0-t}	0.992 [0.934-105.3]	1.034 [1.001-1.068]
$AUC_{0-\infty}$	0.989 [0.932-104.9]	1.048 [1.008-1.090]
Cmax	1.029 [0.948-1.116]	1.039 [0.999-1.082]

AUC_{0-t}: Area under the plasma concentration time curve from time zero to the time of the last measurable concentration, $AUC_{0-\infty}$: Area under the plasma concentration time curve from time zero to infinity, Cmax**:** maximal plasma concentration:

The results (Table 1) indicated that in relation to both olmesartan and amlodipine the fixed-dose combination of olmesartan medoxomil 40 mg and amlodipine 10 mg oral tablet (Formulation G) was bioequivalent to the corresponding dose of co-administered olmesartan medoxomil and the Italian commercially available amlodipine used in the pivotal Phase III efficacy studies.

U111 (Formulation G, Two Doses 10/5 and 40/10)

This study compared the proposed fixed dose combination tablets to olmesartan medoxomil and amlodipine monotherapy tablets using two cohorts, each with 30 subjects for the doses 10/5 and 40/10, the lowest[3] and highest doses. Each cohort used a 2-way cross over design.

Table 2: PK Results from Study CS8663-A-U111

Cohort 1 (Treatments A and B) 10/5	Geometric Mean Ratio (Fixed/Free) and [90% Confidence Intervals]	
	Olmesartan	Amlodipine
AUC_{0-t}	1.076 [0.997-1.161]	1.016 [0.991-1.042]
$AUC_{0-\infty}$	1.074 [0.994-1.160]	1.016 [0.994-1.043]
Cmax	1.143 [1.066-1.225]	0.990 [0.956-1.025]

Cohort 2 (Treatments C and D) 40/10	Geometric Mean Ratio (Fixed/Free) and [90% Confidence Intervals]	
	Olmesartan	Amlodipine
AUC_{0-t}	1.121 [1.033-1.216]	1.016 [0.972-1.062]
$AUC_{0-\infty}$	1.135 [1.047-1.230]	1.012 [0.966-1.060]
Cmax	1.097 [1.018-1.183]	1.083 [1.032-1.136]

The results (Table 2) indicated that both the lower strength (10/5 mg) and higher strength (40/10 mg) doses of the fixed- dose combination formulation intended for commercial use were bioequivalent to the corresponding doses of co-administered olmesartan medoxomil and the Italian commercially available amlodipine used in the pivotal Phase III efficacy studies.

U112 (Formulation G, Dose Proportionality Study)

This study used two cohorts of 30 subjects using proposed fixed-dose combination tablets. Cohort 1 (3-way crossover) received; A 40/10, B 20/5, C 10/10. Cohort 2 (also 3-way crossover) received; D 40/5, E 20/10, F 10/5.

This is strictly a dose-proportionality study using six fixed-dose combinations of olmesartan/amlodipine and such studies are not normally evaluated by the quality evaluator. In this case the study should give information on the interactions between the two drug substances, thus the conclusions of this study have been summarised. They are based on the descriptive pharmacokinetic statistics (from pooled data) and the statistical analyses performed by the sponsor.

- The total systemic exposure of olmesartan (AUC), following oral administration of 10 mg, 20 mg, and 40 mg dose levels increased in a dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of amlodipine.
- The C_{max} values of olmesartan, following oral administration of 10 mg, 20 mg, and 40 mg dose levels, increased in a slightly less than dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of amlodipine.
- The systemic exposure of amlodipine (AUC and C_{max}), following oral administration of 5 mg and 10 mg dose levels, increased in a dose-proportional manner when administered in a fixed-dose combination with 10 mg, 20 mg, or 40 mg of OM.

[3] The company developed 10/5 and 10/10 strength tablets, but do not propose to supply these in Australia.

It follows from these results that there is no pharmacokinetic interaction between the active moieties olmesartan medoxomil, olmesartan and amlodipine.

Study U110 (Formulation G, Food Effect)

This study used the proposed 40/10 fixed-dose combination tablets to determine the effect of food.

Table 3: PK Results from Study CS8663-A-U110

Parameter	Geometric Mean Ratio (Fed/Fasted) and [90% Confidence Intervals]	
	Olmesartan	Amlodipine
AUC_{0-t}	0.872 [0.825-0.921]	1.026 [0.996-1.057]
$AUC_{0-\infty}$	0.878 [0.830-0.930]	1.025 [0.992-1.060]
Cmax	0.939 [0.874-1.008]	0.993 [0.960-1.027]

The results (Table 3) indicated that food does not affect the bioavailability of olmesartan or amlodipine from the proposed 40/10 tablets. However, the AUC is statistically less for olmesartan in the fed state.

E102 (Amlodipine Tablets from the UK, USA and Italy)

This study compared three different formulations of amlodipine monotherapy tablets from the UK, USA and Italy, this later formulation being used in the Phase III clinical studies. None were from Australia. However, the sponsor has used the study results in part to justify not using an Australian amlodipine formulation, thus the conclusion of the study is relevant.

The results indicate that the three different marketed formulations of 10 mg amlodipine (as besylate) are bioequivalent.

Justifications for Not Performing Bioavailability Studies

No data were included comparing the 20/5, 20/10 and 40/5 strengths to the appropriate combination of monotherapy tablets or to the proposed 40/10 tablet. The justification for this was acceptable on both chemical and clinical grounds. The dissolution profile results of these strengths at pH 1.2, 4.5 and 6.8 were similar to the dissolution profile results of the 40/10 strength.

No data were included comparing an Australian registered amlodipine tablet to the Italian commercially available amlodipine tablet used in the Phase III clinical studies. The justification of this was acceptable on both chemical and clinical grounds. It was noted that at the maximum daily dose proposed, amlodipine (as besylate) can be considered BCS Class 1.[4]

Consideration by the Pharmaceutical Subcommittee

Details of this submission were presented at the 130th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC endorsed all questions raised by the quality evaluator and in particular the questions raised in relation to the possible formation of alkyl besylates. The PSC considered the justification for using an overseas formulation of amlodipine tablets in the bioavailability studies acceptable. The PSC had no objections to approval of these products provided all issues were subsequently addressed to the satisfaction of the TGA. This was the case.

[4] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Quality Summary and Conclusions

Approval of the company's application was recommended with respect to chemistry, quality control and bioavailability.

III. Nonclinical Findings

Introduction

The data presented were of an acceptable quality. The pivotal studies examining pharmacokinetics and repeat-dose toxicity were performed according to Good Laboratory Practice (GLP) standards.

The sponsor proposes to market Sevikar tablets, which combine two drugs that act via independent mechanisms to reduce blood pressure (BP). The combination is intended for use by persons above the age of 18 years who require additional blood pressure control beyond that provided by drug monotherapy. The drugs combined in Sevikar tablets are amlodipine, a dihydropyridine-class calcium channel blocker that lowers blood pressure by relaxing smooth muscle in vessel walls, and olmesartan, an inhibitor of the angiotensin AT_1 receptor (activation of which has various blood pressure-raising effects). The choice of drugs used in the combination is based on their pharmacological properties and clinical effectiveness.

Pharmacology

The mechanism of action of the drugs in the combination is well established, and both drugs have a history of extensive research, regulatory review, and postmarket experience. The efficacy of the olmesartan/amlodipine combination was tested in studies using Spontaneously Hypertensive (SH) rats. It was shown that the drug combination produced an additive decrease in BP as compared with drug monotherapy.

No specific studies were submitted investigating potential pharmacodynamic interactions between the drug combination and other drugs.

Pharmacokinetics

The pivotal pharmacokinetic data were obtained as part of an examination of the toxicology of the combination. Pharmacokinetics of both drugs, whether administered alone or in combination, were comparable in both sexes, with the time maximal plasma concentration (T_{max}) generally around 2-4 hours after dosing for both drugs, regardless of dose or repetition number. Amlodipine C_{max} and AUC values increased progressively with dose repetition, with a 2-4-fold increase in $AUC_{0\text{-}24h}$ values after the 90th dose. In contrast, olmesartan AUC values in rats receiving the drug alone at 300 mg/kg/day, showed little or no increase during the dosing period.

Overall, combination treatment had no effect on amlodipine AUC values. However, animals receiving combination dosing showed a marked increase in both C_{max} and AUC values for olmesartan as compared with animals receiving olmesartan medoxomil alone. Olmesartan $AUC_{0\text{-}24h}$ values after the 90th dose of olmesartan medoxomil/amlodipine besylate at 300/30 mg/kg/day were around 6- to 10-fold higher than in animals receiving olmesartan medoxomil at 300 mg/kg/day.

This amlodipine effect on olmesartan exposure was shown to be:

- dependent on the concentrations of both drugs, occurring at amlodipine ≥ 10 mg/kg/day and olmesartan ≥ 100 mg/kg/day, and
- related to a significant drug-induced decrease in intestinal motility that results in markedly higher plasma levels of olmesartan.

This drug-interaction effect was not seen in several clinical studies in which the pharmacokinetics of olmesartan and amlodipine were investigated at the maximum recommended daily dose of 40 mg/10 mg in adult hypertensive patients.

In terms of potential interactions with other drugs, the published literature indicates that amlodipine (which is metabolised by and also inhibits cytochrome P450 [CYP] 3A4) can interact with other drugs that are metabolised by CYP3A4. Olmesartan undergoes little or no metabolism, and is unlikely to interfere with CYP-mediated metabolism of other drugs.

Toxicology

Relative exposure

Exposure ratios were derived by dividing rat $AUC_{0\text{-}24\ h}$ values by $AUC_{0\text{-}\infty}$ values from adult humans given a single dose at the maximum recommended level of olmesartan medoxomil/amlodipine besylate (Table 4). The maximum recommended daily dose of Sevikar for humans is one 40/10 mg tablet (40 mg of olmesartan medoxomil and 10 mg of amlodipine besylate). $AUC_{0\text{-}\infty}$ values were used as the 10-day human pharmacokinetics study did not calculate $AUC_{0\text{-}24\ h}$ values. According to the sponsor, human $AUC_{0\text{-}\infty}$ values after a single dose of the drug combination are equivalent to $AUC_{0\text{-}24\ h}$ values for multiple dosing at steady state, and steady state levels are reached after about 9-days dosing. Two $AUC_{0\text{-}\infty}$ values for both active compounds were provided from studies CS8663-A-U111 and CS8663-A-U109, respectively: olmesartan = 6169 and 5589 ng.h/mL and amlodipine = 350 and 523 ng.h/mL. These values are comparable to those obtained in the longer studies. An average of the two values was used to calculate exposure ratios: olmesartan = 5879 ng.h/mL; amlodipine = 437 ng.h/mL.

Separate exposure ratio values are given in Table 4 for male and female rats at each dose. The values were, however, generally similar for both sexes. Exposure ratio values for olmesartan and amlodipine in the pivotal 13-week toxicology study attained values of around 3-4 at a dosing level of 100/10 mg/kg/day. However, no No Observable Adverse Effect Level (NOAEL) was established in this study due to findings representing exaggerated pharmacology at even the lowest doses.

Single-dose toxicity

The sponsor did not perform single-dose toxicity testing on the olmesartan/amlodipine combination.

Repeat-dose toxicity

Repeat-dose studies used orally administered olmesartan medoxomil/amlodipine besylate combination and were conducted in rats. Animals were dosed once per day by gavage. The studies were performed by an established laboratory, and used both sexes and standard testing times and group numbers. The pivotal 13-week study was performed according to GLP procedures.

A preliminary dose range-finding study demonstrated no deaths or gross pathological changes in rats dosed for 28 consecutive days with up to 300 mg/kg/day of olmesartan medoxomil or up to 30 mg/kg/day of amlodipine besylate. Based on the latter result, groups of rats (n = 15/sex/group) were given a once-daily oral (gavage) dose of olmesartan medoxomil/amlodipine besylate at 100/10 or 300/30 mg/kg/day for 13 weeks. Two other groups of rats were dosed with the individual components at the same dose as was present in the highest dose (HD) combination (olmesartan medoxomil at 300 mg/kg/day and amlodipine besylate at 30 mg/kg/day). Three females from the amlodipine-only group and 1 male and 1 female from the 300/30 groups died during dosing. These animals showed intestinal distension and suppression of body weight gain, and death was attributed to amlodipine-induced peristaltic motion disorder.

Table 4: Relative exposure to olmesartan and amlodipine during rat repeat-dose toxicology studies

Study no.	Dosing duration (sample time)[a]	Drug (dose-mg/kg/ day)	Analyte	Sex	$AUC_{0\text{-}24\ h}$ (ng.h/ mL)	Exposure ratio[b]
APS-152-055	28 days (day 28)	Olmesartan medoxomil (100)	Olmesartan	M	5660	1.0
			Olmesartan	F	6580	1.1
		Olmesartan medoxomil (300)	Olmesartan	M	22600	3.8
			Olmesartan	F	26900	4.6
		Amlodipine besylate (3)	Amlodipine	M	196	0.5
			Amlodipine	F	211	0.5
		Amlodipine besylate (10)	Amlodipine	M	1390	3.2
			Amlodipine	F	1190	2.7
		Amlodipine besylate (30)	Amlodipine	M	7220	17
			Amlodipine	F	6520	15
APS-152-095	90 days (day 90)	Olmesartan medoxomil (300)	Olmesartan	M	22200	3.8
			Olmesartan	F	25500	4.3
		Amlodipine besylate (30)	Amlodipine	M	8090	19
			Amlodipine	F	7930	18
		Olmesartan medoxomil/ Amlodipine besylate (100/10)	Olmesartan	M	20100	3.4
				F	23800	4.1
			Amlodipine	M	1910	4.4
				F	1280	2.9
		Olmesartan medoxomil/ Amlodipine besylate (300/30)	Olmesartan	M	231000	39
				F	166000	28
			Amlodipine	M	9110	21
				F	10400	24

[a]Consecutive days of drug dosing (figure in brackets is day on which analysis of drug pharmacokinetics was performed). [b]AUC value at given dose divided by clinical AUC value at maximum recommended human dose (see text for further details). Human AUC values used were olmesartan = 5879 ng.h/mL; amlodipine = 437 ng.h/mL.

No novel toxicities were observed in the animals dosed with olmesartan medoxomil/amlodipine besylate. The changes seen were generally a summation of the effects found in animals dosed with the individual drugs. There were some changes (for example, colon lumen dilatation) that appeared more pronounced and/or of higher incidence in animals receiving the drug combination. This is not surprising given the marked increase in olmesartan exposure in animals receiving combination as compared with single drug dosing (see above discussion of pharmacokinetics). However, most of the changes seen reflect known pharmacological actions of amlodipine or olmesartan or the class of drugs to which they belong. The changes included:

(1) Thickening of arterial walls (afferent arterioles/interlobular arteries) in the kidney: a known consequence of angiotensin II receptor antagonist treatment that is thought to derive from hyperplasia/hypertrophy of juxtaglomerular cells induced by increased renin production.

(2) Macroscopic distension of the small and/or large intestines: a known side-effect of calcium channel blockers.

(3) Decrease in red blood cell (RBC) parameters: reported previously in rats treated with an angiotensin II receptor antagonist and appears to be a consequence of decreased erythropoietin production.

(4) Decreases in absolute weights of several organs: a secondary consequence of intestinal distension and suppression of body weight gain. Although the sponsor's studies did not establish a NOAEL for the olmesartan medoxomil/amlodipine besylate combination in rats, the apparent absence of novel toxicities, combined with the extensive postmarket experience for both drugs, suggest that there are no novel safety issues of clinical concern.

Genotoxicity, Carcinogenicity, and Reproductive and developmental toxicity

No studies were submitted by the sponsor under these headings, which is acceptable and consistent with the TGA-adopted EU guidelines for fixed dose combinations using previously approved components.[5] Both active substances have been approved and on the market for several years and there is extensive nonclinical and clinical information available. As noted in the proposed product information (PI), Sevikar should not be used during pregnancy, consistent with the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

Paediatric use

Sevikar tablets are not intended for use in children.

Nonclinical Summary and Conclusions

The amlodipine/olmesartan combination produced an additive decrease in BP as compared with drug monotherapy in SH rats.

Toxicokinetic data from a rat 13-week oral study revealed that although amlodipine AUC values were comparable for animals given amlodipine besylate or olmesartan medoxomil/amlodipine besylate, animals receiving combination dosing showed a marked increase in both C_{max} and AUC values (6- to 10-fold) as compared with animals receiving olmesartan medoxomil alone. The interaction between amlodipine besylate and olmesartan medoxomil appeared to be related to a significant drug-induced decrease in intestinal motility. However, no evidence for such an interaction was seen in the human pharmacokinetic data with the combination.

Metabolism, tissue distribution, and excretion studies were not performed by the sponsor. Published results indicate that amlodipine is converted to various metabolites and (in humans) is predominantly excreted in urine, while olmesartan is largely excreted unchanged via faeces.

Studies of possible interaction with other co-medications were not performed by the sponsor. Published results indicate that amlodipine, which is metabolised by and also inhibits CYP3A4, can interact moderately with other drugs that are metabolised by CYP3A4. Olmesartan shows little inhibitory activity towards CYP enzymes and is unlikely to interfere with CYP-mediated metabolism of other drugs.

No novel toxicities were observed in the pivotal rat 13-week, repeat-dose oral study. The changes seen were generally a summation of the effects found in animals dosed with the individual drugs.

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[5] EMEA, Committee for Medicinal Products for Human Use (CHMP), 19 February 2009. Guideline on Clinical Development of Fixed Combination Medicinal Products, CPMP/EWP/240/95 Rev 1.

Most of the changes seen reflected known pharmacological actions of amlodipine or olmesartan or the class of drugs to which they belong. Those changes included thickening of arterial walls in the kidney, macroscopic distension of the small and/or large intestines, a decrease in RBC parameters, and decreases in absolute weights of several organs. No novel toxicities were seen in combination-dosed animals as compared with single component-dosed animals, despite the marked increase in plasma olmesartan levels.

No genotoxicity, carcinogenicity, or reproductive toxicity studies were submitted for Sevikar, which is acceptable and consistent with TGA-adopted EU guidelines for fixed dose combinations using previously approved components. As noted in the proposed PI, Sevikar should not be used in pregnancy due to the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

As both active compounds have been approved and on the market for some years, and as there is extensive nonclinical and clinical data available (for both the compounds alone and as various combinations) there are no novel clinical safety concerns raised by the nonclinical data.

There were no nonclinical objections to the registration of Sevikar tablets for the treatment of hypertension.

IV. Clinical Findings

Introduction

The data presented for evaluation in this application for registration of olmesartan medoxomil/amlodipine (OM/AML) comprised 2 pharmacokinetic interaction studies and 3 controlled efficacy and safety studies. In addition, data from 11 biopharmaceutic studies were submitted, including two studies validating the relevance of the clinical trial data to the fixed combination tablet formulations to be marketed, a food interaction study and a study demonstrating bioequivalence of three different overseas marketed AML monotherapy formulations.

The clinical pharmacology program consisted of 13 pharmacokinetic (PK) studies

- Six bioavailability/bioequivalence studies conducted to determine the appropriate formulation of OM/AML for further development. All six studies used the highest proposed dosages of OM (40 mg) and AML (10 mg).
- A secondary bioavailability/bioequivalence study which evaluated a different strength/formulation of OM/AML fixed-dose combination not selected for further development.
- Six pivotal studies comprising evaluations of:
  the potential for pharmacokinetic interaction between OM and AML

  the effect of food on the bioavailability of olmesartan and AML from the fixed-dose combination,

  dose proportionality using six fixed-dose combinations of OM/AML,

  bioequivalence at the highest and lowest doses (OM/AML 40/10 mg and 10/5 mg) of the fixed-dose combinations with the corresponding separate tablets used in the pivotal Phase III efficacy and safety studies, and

  bioequivalence of three different overseas marketed formulations of AML.

The 3 pivotal clinical efficacy and safety studies included 3233 randomised patients in total, of whom 2892 received treatment with OM/AML combination therapy (746 for at least 9 months overall and 173 for at least 12 months overall). Overall, the studies included 691 elderly patients

aged ≥ 65 years (of whom 83 were aged ≥ 75 years); 613 elderly patients (76 aged ≥ 75 years) were exposed to OM/AML combination therapy.

The three efficacy and safety studies comprised:

- A placebo-controlled factorial-design study which compared OM/AML fixed-dose combinations with their respective individual components (study CS8663-A-U301, subsequently referred to as study 301).The 8-week randomised, double-blind period of study 301 was followed by a 44-week long term open-label treatment period.
- A study which compared 8 weeks of therapy with add-on AML 5 mg and 10 mg versus add-on placebo in patients whose BP was not adequately controlled after 8 weeks of monotherapy with OM 20 mg (study CS8663-AE302, subsequently referred to as study 302).
- A study which compared 8 weeks of therapy with add-on OM 10 mg, 20 mg and 40 mg versus add-on placebo in patients whose BP was not adequately controlled after 8 weeks of monotherapy with AML 5 mg (study CS8663-A-E303, subsequently referred to as study 303). The randomised double-blind period of study 303 was followed first by an 8-week double-blind (but non-randomised) period in which the OM/AML dose was up-titrated in patients requiring further BP control, and then by a 28-week long-term open-label treatment period. This long-term treatment period has now completed, however data that were available at the time of compilation of the submission were up to Week 34, that is, after 10 weeks of open-label treatment.

As previously noted, the sponsor's Clinical Overview was written specifically for the Australian submission. It comprised the European Clinical Overview as well as data from further statistical analyses to support use of Sevikar as initial therapy in the treatment of hypertension. In addition the sponsor also provided a justification for the indication of switching patients who are not adequately controlled on other angiotensin receptor blockers, ACE inhibitors or dihydropyridine CCBs to Sevikar.

Pharmacodynamics

No new pharmacodynamic data were presented for evaluation.

Pharmacokinetics

Six potential formulations (A, B, C, D, G and H) of the OM/AML fixed-dose combination were evaluated in pharmacokinetic studies. Formulation G was selected as the primary formulation for commercial use based on assessment of the pharmacokinetic results, its specific pharmaceutical properties, and the results of stability tests.

Pivotal Clinical Pharmacology Studies

Study CS-8663-A-U101 (Drug-Drug Interaction Study)

Study 101 was a randomised, open-label, 3-way crossover multiple dose study to determine the pharmacokinetic (PK) interaction of olmesartan medoxomil and amlodipine besylate in healthy subjects. The primary objective of this study was to investigate the PK interaction between olmesartan and amlodipine when administered concomitantly in healthy subjects, and the secondary objective was to evaluate the safety and tolerability when the two compounds are administered concomitantly.

Subjects were assigned randomly to receive one of the following treatments on three separate occasions:

- Treatment A: olmesartan medoxomil tablets (1 × 40 mg tablet) administered orally od for 10 days with 240 mL of water

- Treatment B: amlodipine besylate tablets (USA commercially available innovator product 1 × 10 mg tablet) administered orally od for 10 days with 240 mL of water
- Treatment C: olmesartan medoxomil 40-mg tablets and amlodipine besylate 10-mg tablets administered orally od for 10 days with 240 mL of water.

Pharmacokinetic Results

The treatment contrast was constructed from the Analysis of Variance (ANOVA) to obtain the least-squares mean (LSM) difference, and the 90% confidence interval (CI) for the natural log (ln)-transformed treatment difference. For each treatment comparison, no significant drug-drug interaction was concluded if the 90% CI for the mean ratio is within the acceptable range (80.0 to 125.0%) for AUC and the maximal plasma concentration at steady state ($C_{ss,\,max}$).

The ratio of geometric LSM and 90% confidence intervals for AUC and $C_{ss,max}$ of olmesartan and amlodipine were all within the 80.0 to 125.0% limit. Therefore, the concomitant administration of amlodipine besylate (USA commercial innovator product 10 mg tablet) did not affect the rate and extent of exposure of olmesartan (40 mg tablet) under fasting conditions.

Study SE-866/31 (Drug-Drug Interaction Study)

Study 31 assessed the effect of the combination of the oral angiotensin II-antagonist olmesartan medoxomil and amlodipine (USA commercially available innovator product) on pharmacokinetics, safety and tolerability in healthy, male subjects. It was an open-label, randomised, repeated-dose, 3-way crossover study. The primary objective was to evaluate the effects of co-administration of olmesartan medoxomil and amlodipine on the pharmacokinetics of each substance.

Pharmacokinetic Results

Descriptive statistics for pharmacokinetic variables were calculated using appropriate methods. The principal plasma pharmacokinetic parameters calculated for each analyte during the monotherapy and combination therapy periods were compared using a bioequivalence approach. For the area under the plasma concentration time curve at steady state (AUC_{ss}) and $C_{ss,max}$, equivalence was investigated using a two one-sided test approach. For each parameter, 90% confidence intervals were constructed for the ratios of geometric means for each pair of treatment periods. This was accomplished using ANOVA of ln-transformed data. Bioequivalence was inferred if the 90% confidence intervals lay completely within the range 0.8 – 1.25. For t_{max}, a non-parametric approach was used: 90% confidence intervals (Hodges-Lehmann intervals) were constructed for the median of all possible pair-wise differences of the period differences between two sequences. Equivalence was inferred if the confidence interval was entirely included in the range ± 20% of the median t_{max} value for the reference treatment (the monotherapy period). It was stated that the sample size of 18 patients was fixed on a pragmatic basis.

Statistical analysis demonstrated bioequivalence for all key plasma pharmacokinetic parameters between the combination therapy period and the monotherapy period for each analyte. Thus there was no statistically significant pharmacokinetic interaction between olmesartan and amlodipine.

Study CS8663-A-E-102 (Bioequivalence Study of Overseas Marketed Amlodipine Formulations)

Study 102 was a Phase I randomised, open-label, single-dose, three-way crossover study to determine the bioequivalence of 10 mg amlodipine besylate in three overseas (UK, Italy and USA) formulations. The primary objective was to determine the bioequivalence of the three marketed amlodipine besylate formulations. The secondary objective was to assess the safety and tolerability of a single dose of these three marketed amlodipine besylate formulations.

Three amlodipine besylate formulations (each equivalent to 10 mg amlodipine, see below) were investigated in three treatment periods, separated by washout periods of at least 14 days. A total of 18 healthy male or female subjects were assigned to the following treatments:

- Treatment A, UK formulation 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets.
- Treatment B, USA formulation 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets.
- Treatment C, Italian formulation 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets.

Pharmacokinetic Results

Bioequivalence was concluded if ratios of LSMs and 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} fell within 80% (0.80) to 125% (1.25). A non-parametric approach was used to construct 90% CI for untransformed T_{max} values of amlodipine. No statistical tests were made for the other secondary pharmacokinetic parameters.

When amlodipine besylate was administered as an oral tablet in three different formulations, the rate and extent of bioavailability of amlodipine were similar to each other. The mean terminal elimination half-life of amlodipine for the UK, US and Italian formulations were approximately 44, 42 and 42 hours, respectively.

Bioequivalence of amlodipine between the three tablet formulations was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} of amlodipine were within 80% to 125% for all three formulations. Therefore, the rate and extent of bioavailability of amlodipine from the three tablet formulations is bioequivalent under fasting conditions.

The three different marketed formulations of AML (as besylate, equivalent to AML 10 mg) were shown to be bioequivalent. This would support that the conclusions drawn from the bioequivalence/bioavailability studies comparing AML in the OM/AML fixed-dose combination formulation versus the Italian commercially available innovator product are applicable to the other two overseas commercially available formulations of AML (UK and USA formulations). The Italian commercially available innovator product was the formulation of AML used in the pivotal efficacy studies 301, 302 and 303.

Study CS8663-A-U109 (Bioavailability Study for Formulation G)

Study U109 was a single-centre, single-dose, randomised, open-label, 2-way crossover study to determine the bioequivalence of a fixed combination formulation of olmesartan medoxomil and amlodipine besylate, versus the co-administration of the separate entities as their marketed formulations in healthy subjects under fasting conditions. The objective of this study was to determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to co-administration (free combination) of the separate entities as their marketed formulations. This study was also discussed in Section II.

Subjects were randomised to the following treatments:

- Test Treatment: CS-8663 (Formulation G) 1 × 40 mg olmesartan medoxomil/ 10 mg amlodipine besylate fixed combination oral tablet administered orally with 240 mL of water.
- Reference Treatment: 1 × 40 mg olmesartan medoxomil and 1 × 10 mg amlodipine besylate (Italian commercially available innovator product) administered orally with 240 mL of water.

Pharmacokinetic Results

Bioequivalence was concluded if the 90% CIs of the ratios of geometric means for AUC_{0-t}, AUC_{0-inf}, and C_{max} fell within 80.0% to 125.0%.

A non-parametric approach was used to construct 90% CI for T_{max} values of olmesartan and amlodipine. The Hodges-Lehmann estimator between the Test and Reference formulations (Test - Reference) was presented and the CIs were generated using the Moses method.

When olmesartan medoxomil was administered in a fixed-dose combination with amlodipine (Formulation G), the rate and extent of bioavailability of olmesartan were similar to those observed when olmesartan medoxomil was co-administered with amlodipine (Italian commercially available innovator product) as separate tablets (Table 1, Section II). Mean terminal elimination half-life of olmesartan for the Test and Reference products were 10.7 and 11.7 hours, respectively.

An ANOVA model was used to determine the bioequivalence of olmesartan between the two treatment regimens. The ratio of LSM and 90% CIs for AUC, AUC_{0-inf}, and C_{max} of olmesartan were within 80.0 to 125.0%. Therefore, rate and extent of bioavailability of olmesartan from the fixed-dose combination (Formulation G) is bioequivalent to the co-administration of olmesartan medoxomil 40 mg and amlodipine (Italian commercially available innovator product) 10 mg tablets under fasting conditions.

Study CS8663-A-U110 (Definitive Food Effect Study using Formulation G)

This was a single-centre, single-dose, randomised, open-label, 2-way crossover study to determine the effect of food on the bioavailability of olmesartan medoxomil and amlodipine besylate of a fixed combination formulation in healthy adult subjects. This study was also discussed in Section II.

During each dosing period, subjects were confined to the clinical pharmacology unit on Day -2 through completion of the 144-hour post-dose procedures on Day 7. There was a 21-day washout between treatment periods. Subjects were randomised to the following treatments:

- Test: (Treatment A) CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally within 30 minutes following the start of a high-fat breakfast. An approximate 10-hour overnight fast preceded the high-fat breakfast.
- Reference (Treatment B) CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally with 240 mL of water, following a minimum 10-hour overnight fast.

Pharmacokinetic Results

Absence of food effect was concluded if the 90% CIs of the ratios of geometric means for AUC_{0-t}, AUC_{0-inf} and C_{max} fell within 80.0% to 125.0%.

The overall extent of bioavailability (AUC_{0-inf}) of olmesartan was slightly lower (12.1%) when CS-8663 was administered with a high-fat breakfast than after a minimum 10 hour overnight fast (geometric means of 5401.5 versus 6143.9 ng·h/mL, respectively) (Table 3, Section II). Similarly, the rate of bioavailability (C_{max}) was slightly lower by about 6.93% and the median time to reach peak plasma concentrations appeared to be delayed by approximately 30 minutes. The mean terminal elimination half-life of olmesartan was similar when administered under fed and fasting conditions (approximately 14.2 hours).

The rate and extent of bioavailability of amlodipine was similar when CS-8663 was administered with or without food (Table 3, Section II). The mean terminal elimination half-life of amlodipine was approximately 40 hours for both treatments.

The effect of food on the bioavailability of olmesartan and amlodipine was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan were bioequivalent after oral administration of CS-8663 under fed and fasting conditions.

Since food did not affect the PK profiles of the fixed combination, the presence of food should not alter efficacy results with Formulation G (to be marketed).

Study CS8663-A-U111 (Bioavailability Study Evaluating Fixed-Dose Combinations Intended for Commercial Use – Formulation G)

Study 111 was a parallel-group, open-label, randomised, crossover study to determine the bioavailability of a fixed- dose combination tablet of olmesartan medoxomil and amlodipine besylate relative to olmesartan medoxomil and amlodipine (Italian commercially available innovator product) tablets in healthy subjects. The objective of this study was to determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation intended for commercial use relative to co-administration of the separate entities as their marketed formulations. This study was also discussed in Section II.

The bioavailability was determined for the following 2 tablet strengths:

- olmesartan 10 mg and amlodipine 5 mg
- olmesartan 40 mg and amlodipine 10 mg.

Subjects were randomised to the following treatments:

Cohort 1:

- Treatment A (Test): CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg] administered orally with 240 mL of water.
- Treatment B (Reference): Olmesartan medoxomil 10 mg in combination with amlodipine besylate 5 mg (Italian commercially available innovator product). A single oral dose of 1 x 10 mg olmesartan medoxomil and 1 x 5 mg amlodipine besylate (Italian commercially available innovator product) administered orally with 240 mL of water.

Cohort 2:

- Treatment C (Test): CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally with 240 mL of water.
- Treatment D (Reference): Olmesartan medoxomil 40 mg in combination with amlodipine besylate 10 mg (Italian commercially available innovator product). A single oral dose of 1 x 40 mg olmesartan medoxomil and 1 x 10 mg amlodipine besylate (Italian commercially available innovator product) administered orally with 240 mL of water.

Pharmacokinetic Results

Bioequivalence was concluded if the 90% CIs of the ratios for the comparison of Treatment A/Treatment B and Treatment C/Treatment D for AUC_{0-t}, AUC_{0-inf} and C_{max} fell within 80.0% to 125.0%. A non-parametric approach was used to construct 90% CI for T_{max} values of olmesartan and amlodipine per cohort. The Hodges-Lehmann estimator between the Test and Reference formulations (Test - Reference) was presented and the CIs were generated using the Moses method.

When olmesartan medoxomil was administered in a fixed-dose combination with amlodipine besylate (10 and 5 mg, respectively), the rate and extent of bioavailability of olmesartan was similar to that observed when olmesartan medoxomil 10 mg was coadministered with 5 mg amlodipine (Italian commercially available innovator product) as separate tablets (Table 2, Section II). The

mean terminal elimination half-life of olmesartan for the Test and Reference treatments were similar 14.328 and 13.639 hours, respectively.

Bioequivalence of olmesartan between the Test and Reference products was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan from the fixed-dose combination tablet is bioequivalent to olmesartan medoxomil 10 mg tablets when coadministered with 5 mg amlodipine (Italian commercially available innovator product) tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 15.9 to 17.5%.

When olmesartan medoxomil was administered in a fixed-dose combination with amlodipine besylate (40 and 10 mg, respectively), the rate and extent of bioavailability of olmesartan were similar to those observed when olmesartan medoxomil 40 mg was coadministered with 10 mg amlodipine (Italian commercially available innovator product) as separate tablets (Table 2, Section II). The mean terminal elimination half-life of olmesartan for the Test and Reference treatments were similar 15.630 and 17.273 hours, respectively.

Bioequivalence of olmesartan between the Test and Reference products was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan from the fixed-dose combination tablet is bioequivalent to olmesartan medoxomil 40 mg tablets when coadministered with 10 mg amlodipine (Italian commercially available innovator product) tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 16.8 to 18.1%.

When amlodipine besylate was administered in a fixed-dose combination with olmesartan medoxomil (5 and 10 mg, respectively), the rate and extent of bioavailability of amlodipine were similar to those observed when 5 mg amlodipine (Italian commercially available innovator product) was coadministered with olmesartan medoxomil 10 mg as separate tablets (Table 2, Section II). The mean terminal elimination half-life of amlodipine for the Test and Reference treatments were similar 40.74 and 40.46 hours, respectively.

Bioequivalence of amlodipine between the Test and Reference products was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} of amlodipine were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine from the fixed-dose combination tablet were bioequivalent to 5 mg amlodipine (Italian commercially available innovator product) tablets when coadministered with olmesartan medoxomil 10 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 5.7 to 7.9%.

When amlodipine besylate was administered in a fixed-dose combination with olmesartan medoxomil (10 and 40 mg, respectively), the rate and extent of bioavailability of amlodipine were similar to those observed when 10 mg amlodipine (Italian commercially available innovator product) was coadministered with olmesartan medoxomil 40 mg as separate tablets (Table 2, Section II). The mean terminal elimination half-life of amlodipine for the Test and Reference treatments were similar, 40.24 and 40.79 hours, respectively.

Bioequivalence of amlodipine between the Test and Reference products was assessed using an ANOVA model. The ratio of LSM and 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} of amlodipine were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine from the fixed-dose combination tablet were bioequivalent to 10 mg amlodipine (Italian commercially available innovator product) tablets when coadministered with olmesartan medoxomil 40 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 9.7 to 10.5%.

Study CS8663-A-U112 (Dose Proportionality Study)

Study 112 was a parallel-group, randomised, open-label, single-dose, 3-period crossover study to determine the dose proportionality of olmesartan and amlodipine from different strengths of an olmesartan medoxomil and amlodipine besylate fixed dose combination tablet when administered to healthy subjects. The objective of this study was to determine the dose proportionality of olmesartan and amlodipine from different strengths of olmesartan medoxomil and amlodipine besylate fixed-dose combination tablet intended for commercialization. This study was also discussed in Section II. Dose proportionality was determined for the following 6 tablet strengths:

- olmesartan medoxomil 40 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 20 mg and amlodipine besylate 5 mg
- olmesartan medoxomil 10 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 40 mg and amlodipine besylate 5 mg
- olmesartan medoxomil 20 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 10 mg and amlodipine besylate 5 mg.

Subjects were randomized to the following treatments:

Cohort	Treatment	Olmesartan Medoxomil (mg)	Amlodipine Besylate (mg)
1	A	40	10
	B	20	5
	C	10	10
2	D	40	5
	E	20	10
	F	10	5

Pharmacokinetic Results

Since there were three dose levels of olmesartan, an Analysis of Covariance (ANCOVA) was performed on the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf} and C_{max} using a Power Model approach. Dose proportionality was to be declared if the 95% CI of the regression coefficient (that is, slope estimate) for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} on ln(dose) fell within an acceptable range of 0.75 to 1.25. Since there were only 2 dose levels of amlodipine, original sequences needed to be re-coded to allow pooling of amlodipine data (that is, dose levels). Pooling of the data was allowed if no drug interaction was shown. Bioequivalence with respect to the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} was to be concluded if the 90% CI of the ratio of the geometric LSMs fell within 80.0% to 125.0%. No interaction was to be assumed if the treatments were deemed bioequivalent. Dose proportionality was to be declared if the 90% CI of the ratio of the geometric means (using the appropriate contrast for the 10 mg vs. 5 mg comparison) for dose-normalized AUC_{0-t}, AUC_{0-inf} and C_{max} fell within the equivalent range of 80.0% to 125.0%. At all dose levels, the ratio of AUC_{0-t}/AUC_{0-inf} was approximately 98%, indicating that olmesartan samples were collected during an appropriate interval on the study. The mean terminal elimination half-life of olmesartan ranged from 14.021 to 15.054 hours across all three dose levels.

The slope estimates for each PK parameter along with their respective 95% confidence intervals from the two cohorts pooled together were within the established 0.75 – 1.25 limit. As a result, the systemic exposure of olmesartan following oral administration of 10, 20 and 40 mg dose levels increased in a dose proportional manner when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine. The CI around the slope estimate of C_{max} was not entirely within the pre-specified 0.75 - 1.25 limit. A less than proportional increase in C_{max} was observed for olmesartan

following oral administration of 10, 20 and 40 mg dose levels when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine.

The mean terminal elimination half-life was 51.64 and 48.41 hours, respectively, for the 10 mg and 5 mg amlodipine dose levels. Prior to pooling the data for the dose proportionality assessment, the possibility of a drug interaction was assessed using the bioequivalence approach. Treatments were deemed bioequivalent and no interaction was assumed since the 90% CI of the ratio of the geometric LSMs fell within 80.0% to 125.0%.

Analyses of Variance were performed on the ln-transformed dose-normalised pharmacokinetic parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max}. Confidence intervals around the ratio of LSM for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} for amlodipine were within the 80.0 – 125.0% limit. Overall, the $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} of amlodipine following oral administration of a 5 and 10 mg dose level increased in a dose-proportional manner when administered in a fixed-dose combination with 10, 20 or 40 mg of olmesartan.

Comment

For all formulations evaluated, the pharmacokinetic profiles of OM and AML were essentially unaffected by tablet type and mode of administration. No pharmacokinetic interactions were observed following concomitant administration of OM and AML. Study 101 demonstrated that co-administration of OM and AML did not affect the steady-state maximum and total exposure of either compound at their highest indicated doses (OM 40 mg and AML 10 mg) and under fasting conditions. Study 31 likewise showed no pharmacokinetic interaction between lower doses of OM (20 mg) and AML (5 mg) under fasting conditions.

The purpose of study 102 was to determine the bioequivalence of the following three AML formulations currently marketed in the UK, US and Italy. The three different marketed formulations of AML (as besylate, equivalent to AML 10 mg) that were tested were shown to be bioequivalent. This indicates that the conclusions drawn from the bioequivalence/bioavailability studies comparing AML in the OM/AML fixed-dose combination formulation versus amlodipine (Italian commercially available innovator product) are applicable to the other two overseas commercially available formulations of AML. In the pivotal efficacy studies 301, 302 and 303 amlodipine (Italian commercially available innovator product) was the formulation of AML used.

The bioavailabilities of olmesartan and amlodipine were shown to be unaffected by food (Olmetec and Norvasc Australian PI). Study 110 demonstrated that the pharmacokinetics of olmesartan and amlodipine were equivalent when OM and AML were administered as a fixed-dose combination (OM/AML 40/10 mg; Formulation G) during the fasting state and following a high fat meal. Since food did not affect the PK profiles of the fixed-dose combination, the presence or absence of food should not alter efficacy results with Formulation G (the formulation proposed for marketing).

The total systemic exposure of olmesartan (AUC), following oral administration of 10 mg, 20 mg and 40 mg dose levels, increased in a dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of AML. The olmesartan C_{max} values, following oral administration of OM 10 mg, 20 mg and 40 mg dose levels, increased in a slightly less than dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of AML; however this observation is not considered likely to be of clinical significance.

No information was provided to compare the Australian formulation of Norvasc and the formulations used in the submission.

Efficacy

Study CS8663-A-U301

Study Design and Objectives

Study 301 was a factorial-design, placebo-controlled study which compared OM/AML fixed-dose combinations with their respective individual components. It comprised a 1 – 2 week screening period in which any previous antihypertensive medication was discontinued (Period I), an 8-week factorial design, randomised, double-blind, parallel-group period (Period II), and a long term (44-week) open-label extension period (Period III). Patients were eligible for randomisation into Period II if they had mild to severe hypertension, (mean seated diastolic blood pressure [SeDBP] 95 – 120 mmHg following washout of any previous antihypertensive medication, and if they met all other study entry criteria. The 8-week double-blind period of the study (Period II) included 12 parallel treatment groups:

Placebo	OM/AML 10/5 mg
OM 10 mg	OM/AML 20/5 mg
OM 20 mg	OM/AML 40/5 mg
OM 40 mg	OM/AML 10/10 mg
AML 5 mg	OM/AML 20/10 mg
AML 10 mg	OM/AML 40/10 mg

After completing Period II, patients entering the open-label period (Period III) initially received OM/AML 40/5 mg. The dose was up-titrated (to OM/AML 40/10 mg, followed by addition of hydrochlorothiazide (HCT) 12.5 mg then 25 mg as needed) in patients who did not reach their blood pressure goal (that is, who had SeDBP ≥ 90 mmHg or seated systolic blood pressure [SeSBP] ≥ 140 mmHg) at the previous dose.

The primary objective during Period II (Day 1 to Week 8) was to demonstrate that OM + AML co-administration was more efficacious for seated diastolic blood pressure (SeDBP) lowering than each of its corresponding monotherapy components.

During Period II (Day 1 to Week 8) secondary objectives were:

- To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) lowering with co-administration of various doses of OM + AML compared to their corresponding monotherapy components.
- To evaluate the number (%) of patients achieving their blood pressure goal (defined as blood pressure <140/90 mmHg, <130/80 mmHg for diabetic patients).
- To characterise the pharmacokinetic interactions and corresponding pharmacodynamic correlation (that is, blood pressure lowering) between OM and AML using population pharmacokinetic sampling and modelling (blood specimens collected at selected clinical sites).
- To perform exploratory evaluations of various doses of OM + AML on surrogate markers of cardiovascular risk (high-sensitivity C-reactive protein [hsCRP], metalloproteases 2 and 9, tissue plasminogen activator [tPA], plasminogen activator inhibitor-1 [PAI-1], and microalbuminuria).

During Period III (Week 8 through Week 52) objectives were:

- To gain long-term efficacy and safety experience with co-administration of OM + AML (plus the addition of hydrochlorothiazide [HCT], if needed) while minimally treating patients to their blood pressure goal (<140/90 mmHg, <130/80 mmHg for diabetic patients).
- To evaluate the number (%) of patients achieving their blood pressure goal (defined as blood pressure <140/90 mmHg, <130/80 mmHg for diabetic patients).

At Visit 1, patients naïve to antihypertensive medications who had a mean SeDBP ≥ 95 mmHg and ≤120 mmHg, and who met all other entry criteria, proceeded directly to Visit 3 within 7 days (±3 days). Patients naïve to antihypertensive medication who did not have a mean SeDBP ≥95 mmHg and ≤120 mmHg were discontinued from the study. Patients who had never been on antihypertensive medication or who had not been on antihypertensive medications for at least 2 weeks prior to Visit 1 were considered to be naïve patients.

At Visit 1, patients on antihypertensive medications who met all other entry criteria began a washout of these medications. Patients either immediately stopped antihypertensive medications or down-titrated antihypertensive medications over a period of time determined by the investigator. All of these patients had a blood pressure evaluation 7 days (±3 days) after their last dose of antihypertensive medication (Visit 2).

To be eligible for randomisation, all patients had to have a mean SeDBP ≥95 mmHg and ≤120 mmHg at Visit 3 (the randomisation visit). In addition, the difference in mean SeDBP measurements from Visits 1 and 3 for patients naïve to antihypertensive medication, and from Visits 2 and 3 (or Visits 2.1 and 3) for patients previously on antihypertensive medications, must have been ≤10 mmHg.

Statistical Methods

The statistical methods described below are applicable to the double-blind treatment period only.

The primary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeDBP at Week 8 with the last observation carried forward (LOCF) in the Intent-to-Treat (ITT) population was evaluated using Hommel's procedure in order to control the overall one-sided Type I error rate at 0.025. Hommel's procedure is based on the principle of closed test procedures and utilizes the larger p-value from each pair of p-values obtained from comparing each combination therapy with its respective monotherapy components. These 6 p-values were ordered and Hommel's procedure was applied to determine whether a combination therapy could be concluded as better than both of its individual components. The secondary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeSBP at Week 8 with LOCF in the ITT population was evaluated similarly. One-sided p-values for testing the primary and secondary null hypotheses were derived from an Analysis of Covariance (ANCOVA) model that had fixed effects for treatment group, diabetic status (with or without diabetes) and age group (age ≥65 years or age <65 years), and study baseline blood pressure as a covariate.

This ANCOVA model was also used for the comparison of each monotherapy against placebo. In addition, the number and percentage of patients achieving their blood pressure goal at Week 8 with LOCF within each treatment group and in total were presented. A chi-square test was used to test for significant differences among treatment groups. The Cochran-Mantel-Haenszel test stratified by age group and diabetic status was used to obtain p-values for testing the combination therapy against each of its respective monotherapy components. Hommel's procedure was applied to the set of 6 p-values to determine whether combination therapy was better than both of its individual components in the number and percentage of patients achieving their blood pressure goal. To explore the effect of treatment on inflammatory markers, results from an ANCOVA model with treatment as a fixed effect and baseline as a covariate were presented for change from baseline to Week 8 with LOCF.

Multiplicity

Control of the Type I error level at a one-sided significance level of 0.025 was achieved through the application of Hommel's multiple comparison procedure.

Study Population

A total of 4234 patients were screened, of which 2294 were not entered into the randomised treatment period. The major reason for discontinuation prior to randomisation was inclusion/exclusion criteria not met in 42.5% of cases. A total of 1940 patients were randomised to double-blind treatment; 251 (12.9% of 1940 randomised) of these patients discontinued during Period II. Of the 251 patients who discontinued during Period II, almost half (45%) withdrew due to adverse events. One hundred and fourteen (5.9% of the 1940 randomised) patients withdrew due to adverse events, 43 (2.2%) patients requested to be removed from the study, 37 (1.9%) patients were lost to follow-up, 8 (0.4%) patients met the study withdrawal criteria, 7 (0.4%) patients were removed from the study for taking restricted medications, 6 (0.3%) patients were removed from the study by the investigator, and 36 (1.9%) patients were removed from the study for other reasons. For patients who withdrew due to adverse events, there were no particular clusters or patterns of adverse events noted.

The treatment groups were comparable with respect to demographics, with no statistically significant differences among the treatment groups. Of the 1940 patients in the All Randomized Patients population, 1054 (54.3%) were male, 1385 (71.4%) were Caucasian, 481 (24.8%) were Black, 36 (1.9%) were Asian, and 48 (2.5%) were all other races (including Other, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander). The mean age was 54.0 years. A total of 384 (19.8%) patients were ≥ 65 years of age. Weight, height, and body mass index (BMI) were also similar for the treatment groups, with no statistically significant differences among the treatment groups for these baseline characteristics. Mean weight was 95.1 kg, mean height was 170.1 cm, and mean BMI was 33.5 kg/m^2. A total of 64.7% of patients were obese (BMI ≥ 30 kg/m^2), and 13.5% of patients had diabetes. Approximately one-third of patients were not taking an antihypertensive medication at the time of screening [666 (34.3%)].

In the final case study report baseline values of blood pressure and heart rate were presented for the Safety Population. The treatment groups were similar with respect to baseline values for blood pressure and heart rate, with no statistically significant differences among the treatment groups. At baseline, for the Safety population overall, mean SeDBP was 101.6 mmHg, mean SeSBP was 163.8 mmHg, and the mean heart rate was 76.8 beats per minute (bpm).

The treatment groups were similar with respect to baseline hypertension class, with over 70% of patients in each treatment group having Stage 2 hypertension (defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg). Overall, a total of 1538 (79.3%) patients had Stage 2 hypertension.

Efficacy Results

The patients who entered into study 301 were not currently on antihypertensive treatment at screening (and labelled as naïve for analysis), or had a wash out period of their prior antihypertensive treatment. Therefore, the efficacy data from study 301 represents the antihypertensive effects of initial therapy with the combination regimen compared to initial therapy with each component monotherapy.

Change in Seated Diastolic Blood Pressure from Baseline

Mean reductions in seated DBP were numerically larger in the combination therapy groups than in the monotherapy groups. In the combination therapy groups with AML 5 mg and 10 mg, increasing doses of OM (10 mg, 20 mg, and 40 mg) resulted in numerically larger mean reductions in seated DBP. Combination therapy with OM 10 mg, 20 mg, or 40 mg and AML 5 mg or 10 mg reduced seated DBP to a greater extent than monotherapy with each of the component drugs that made up the combination. The comparisons of the mean reductions in DBP between the combination therapies and the individual component monotherapies were statistically significant, and likely to be clinically meaningful. Mean reduction in SeDBP from baseline to Week 8 is presented in Figure 1.

Table 5 presents the comparisons of combination therapy with the component monotherapies in mean change in seated DBP from baseline to Week 8 with LOCF. The mean reduction in seated DBP was statistically significantly larger for each combination therapy than for the component monotherapies.

The results for mean change in seated DBP at Week 2 were similar to those at Week 8 with LOCF. Mean reductions in seated DBP were numerically larger in the combination therapy groups than in the monotherapy groups. The mean reduction in seated DBP was statistically significantly larger for each combination therapy than for the component monotherapies.

For all active treatment groups, the mean change in seated SBP from baseline to Week 8 with LOCF was statistically significant. Mean reductions in seated SBP were numerically larger in the combination therapy groups than in the monotherapy groups. Combination therapy with OM 10 mg, 20 mg, or 40 mg and AML 5 mg or 10 mg reduced seated SBP to a greater extent than monotherapy with each of the component drugs that made up the combination. The comparisons of the mean reductions in SBP between the combination therapies and the individual component monotherapies were all highly statistically significant, and likely to be clinically meaningful.

Figure 1: Study CS8663-A-U301 - Mean reduction in SeDBP (mmHg) from baseline to Week 8 (FAS, LOCF)

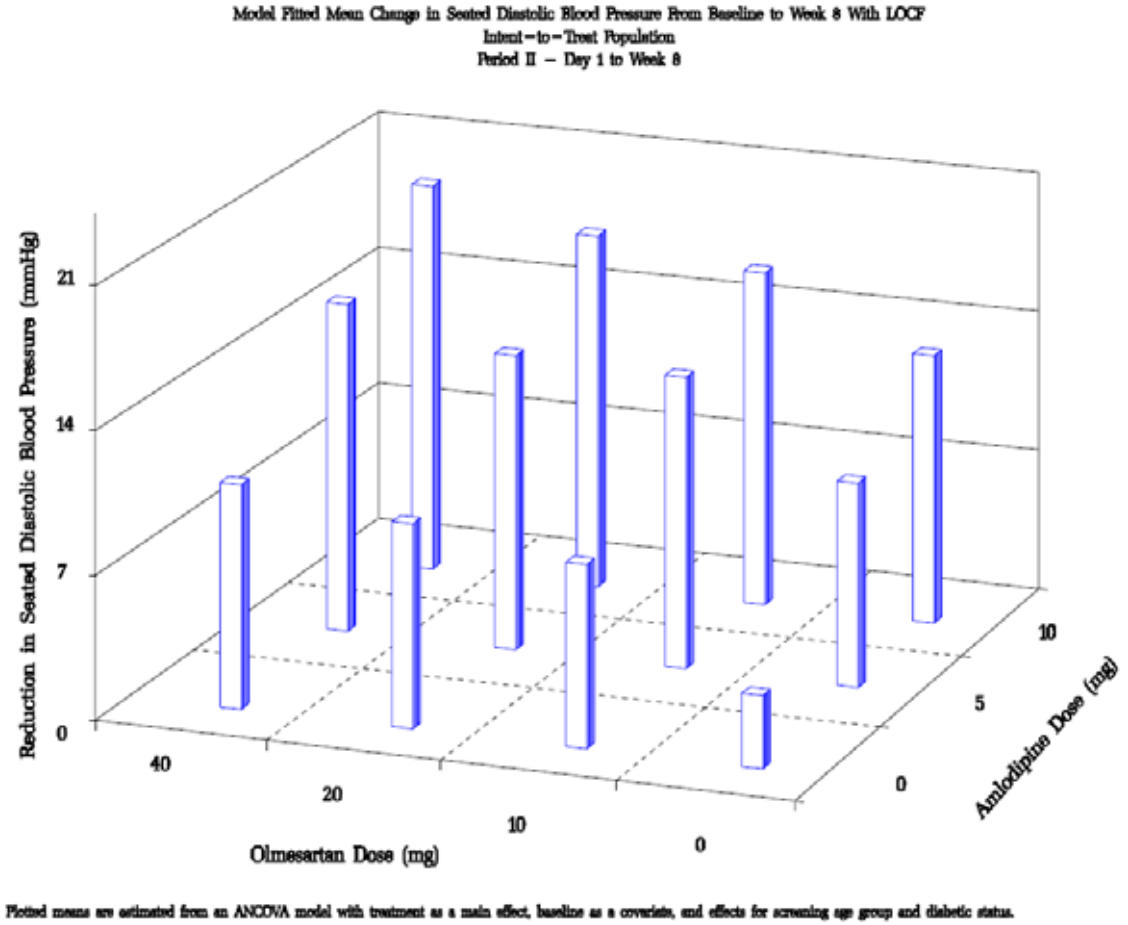


Table 5: Study CS8663-A-U301 – Mean Change in SeDBP (mmHg) from baseline to Week 8 with LOCF – Combination Therapy versus Monotherapy Comparisons – Period II

Treatment comparison		N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)			
Tmt 1	**Tmt 2**	**Tmt 1**	**Tmt 2**	**Tmt 1**	**Tmt 2**	**LS Mean (SE)**	**95%CI**	**p-value**	**Adjusted p-value**
OM10/AML5	OM10	163	160	-14.3 (0.74)	-8.8 (0.75)	-5.5 (0.99)	(-7.4, -3.5)	<0.0001	<0.0001
	AML5		161		-10.0 (0.75)	-4.3 (0.99)	(-6.3, -2.4)	<0.0001	
OM20/AML5	OM20	160	159	-14.6 (0.75)	-9.9 (0.75)	-4.7 (1.00)	(-6.6, -2.7)	<0.0001	<0.0001
	AML5		161		-10.0 (0.75)	-4.6 (0.99)	(-6.5, -2.6)	<0.0001	
OM40/AML5	OM40	157	160	-16.3 (0.76)	-10.9 (0.75)	-5.4 (1.00)	(-7.3, -3.4)	<0.0001	<0.0001
	AML5		161		-10.0 (0.75)	-6.3 (1.00)	(-8.2, -4.3)	<0.0001	
OM10/AML10	OM10	161	160	-16.7 (0.75)	-8.8 (0.75)	-7.8 (0.99)	(-9.8, -5.9)	<0.0001	0.0004
	AML10		163		-13.3 (0.74)	-3.3 (0.99)	(-5.3, -1.4)	0.0004	
OM20/AML10	OM20	158	159	-17.7 (0.75)	-9.9 (0.75)	-7.8 (1.00)	(-9.8, -5.9)	<0.0001	<0.0001
	AML10		163		-13.3 (0.74)	-4.4 (0.99)	(-6.3, -2.4)	<0.0001	
OM40/AML10	OM40	161	160	-19.4 (0.74)	-10.9 (0.75)	-8.5 (0.99)	(-10.5, -6.6)	<0.0001	<0.0001
	AML10		163		-13.3 (0.74)	-6.1 (0.99)	(-8.0, -4.2)	<0.0001	

Table 6 presents the comparisons of combination therapy with the component monotherapies in mean change in seated SBP from baseline to Week 8 with LOCF. The mean reduction in seated SBP was statistically significantly larger for each combination therapy than for the component monotherapies.

Table 6: Study CS8663-A-U301 – Mean Change in SeSBP (mmHg) from baseline to Week 8 with LOCF – Combination Therapy versus Monotherapy Comparisons – Period II

Treatment comparison		N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)			
Tmt 1	**Tmt 2**	**Tmt 1**	**Tmt 2**	**Tmt 1**	**Tmt 2**	**LS Mean (SE)**	**95%CI**	**p-value**	**Adjusted p-value**
OM10/AML5	OM10	163	160	-22.6 (1.23)	-10.9 (1.24)	-11.7 (1.64)	(-14.9, -8.5)	<0.0001	<0.0001
	AML5		161		-14.3 (1.24)	-8.2 (1.63)	(-11.4, -5.0)	<0.0001	
OM20/AML5	OM20	160	159	-22.6 (1.24)	-12.8 (1.25)	-9.9 (1.65)	(-13.1, -6.7)	<0.0001	<0.0001
	AML5		161		-14.3 (1.24)	-8.3 (1.64)	(-11.5, -5.1)	<0.0001	
OM40/AML5	OM40	157	160	-25.1 (1.26)	-15.4 (1.24)	-9.7 (1.65)	(-12.9, -6.5)	<0.0001	<0.0001
	AML5		161		-14.3 (1.24)	-10.8 (1.65)	(-14.0, -7.6)	<0.0001	
OM10/AML10	OM10	161	160	-24.8 (1.24)	-10.9 (1.24)	-13.9 (1.64)	(-17.1, -10.7)	<0.0001	0.0002
	AML10		163		-18.9 (1.23)	-5.9 (1.63)	(-9.1, -2.7)	0.0002	
OM20/AML10	OM20	158	159	-28.1 (1.25)	-12.8 (1.25)	-15.4 (1.65)	(-18.6, -12.1)	<0.0001	<0.0001
	AML10		163		-18.9 (1.23)	-9.2 (1.64)	(-12.5, -6.0)	<0.0001	
OM40/AML10	OM40	161	160	-28.5 (1.24)	-15.4 (1.24)	-13.0 (1.64)	(-16.3, -9.8)	<0.0001	<0.0001
	AML10		163		-18.9 (1.23)	-9.6 (1.63)	(-12.8, -6.4)	<0.0001	

The results for mean change in seated SBP at Week 2 were similar to those at Week 8 with LOCF. Mean reductions in seated SBP were numerically larger in the combination therapy groups than in

the monotherapy groups. The mean reduction in seated SBP was statistically significantly larger for each combination therapy than for the component monotherapies.

Percentage of Patients Who Reached Their Blood Pressure Goal

The percentages of patients who reached their blood pressure goal were higher in the OM + AML combination therapy groups than in the corresponding monotherapy groups.

The percentage of patients in each treatment group who reached their blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) at Week 8 with LOCF and Week 2 were calculated. Approximately 50% of patients on one of the higher dose combination therapies (OM 10 mg + AML 10 mg, OM 20 mg + AML 10 mg, OM 40 mg + AML 5 mg, or OM 40 mg + AML 10 mg) reached their blood pressure goal at Week 8 with LOCF. The proportion of patients who reached their blood pressure goal on each of the combination therapies was statistically significantly higher than the proportion of patients who reached their blood pressure goal on the component monotherapies ($p<0.01$ for all comparisons).

The percentages of patients who reached their blood pressure goal at Week 2 was numerically higher in the combination therapy groups than in the corresponding monotherapy groups. The treatment comparisons of blood pressure goal rate between the combination therapies and the component monotherapies were statistically significant with the exceptions of OM 20 mg + AML 5 mg versus OM 20 mg (31.8 % vs. 22.2 %; p=0.0572) and OM 40 mg + AML 5 mg versus OM 40 mg (38.2 % vs. 31.2 %; p=0.1053). Trough-to peak ratios for SeDBP and SeSBP in the OM/AML combination groups were available for 531 evaluable patients in the pharmacokinetics sub-group of study 301, and were in the range 0.71-0.82, indicating a sustained effect of treatment throughout the 24 hour dose interval.

Probability of Reaching Blood Pressure Thresholds as a Function of Baseline Blood Pressure

Additional efficacy analysis based on the FDA guidance "Points to consider in generating graphs for initial therapy with combination antihypertensive drugs" were performed to support for the indication of initial therapy in the US. From these analyses, an estimated probability of a patient to achieve a set BP goal based on their BP at the initiation of treatment can be made.

For baseline DBP values ranging from 90 mmHg to 115 mmHg, the estimated probability of reaching a DBP <90 mmHg was higher with OM 40 mg + AML 10 mg combination therapy than with either monotherapies (OM 40 mg or AML 10 mg).

For patients with a baseline DBP of 100 mmHg, the estimated probability of reaching DBP < 90 mmHg at Week 8 was:

85.0 % with OM 40 mg + AML 10 mg combination therapy,
71.1 % with OM 20 mg + AML 5 mg combination therapy,
59.8 % with AML 10 mg monotherapy and
50.8 % with OM 40 mg monotherapy.

For patients with a same baseline DBP of 100 mmHg, the estimated probability of reaching DBP < 80 mmHg at Week 8 was considerably lower than reaching DBP < 90 mmHg.

36.8 % with OM 40 mg + AML 10 mg combination therapy,
18.1 % with OM 20 mg + AML 5 mg combination therapy,
12.3 % with AML 10 mg monotherapy and
19.2 % with OM 40 mg monotherapy.

For baseline SBP values ranging from 140 mmHg to 190 mmHg, the estimated probability of reaching a SBP < 130 mmHg was higher with OM 40 mg + AML 10 mg combination therapy than with either monotherapies (OM 40 mg or AML 10 mg).

For patients with a baseline SBP of 160 mmHg, the estimated probability of reaching SBP < 140 mmHg at Week 8 was:

67.7 % with OM 40 mg + AML 10 mg combination,
62.8 % with OM 20 mg + AML 5 mg combination therapy,
47.8 % with OM 40 mg monotherapy and
46.0 % with AML 10 mg monotherapy.

Whereas, for patients with the same baseline SBP of 160 mmHg, the estimated probability of reaching SBP < 130 mmHg at Week 8 was lower than reaching SBP < 140 mmHg. The estimated probability was:

44.2 % with OM 40 mg + AML 10 mg combination therapy,
26.1 % with OM 20 mg + AML 5 mg combination therapy,.
23.4 % with OM 40 mg monotherapy and
20.8 % with AML 10 mg monotherapy.

Secondary Efficacy Variables

The results for decrease from baseline in SeSBP were consistent with those for SeDBP. Thus decreases in SeSBP from baseline to Week 8 were significant for each treatment group ($p < 0.0001$ except $p = 0.0235$ for the placebo group), with the extent of the change generally increasing with increasing dose of each compound. The differences between each combination and its respective monotherapy components were statistically significant and clinically relevant in every case.

Results for SeDBP and SeSBP at intermediate time points (Weeks 2, 4 and 6) demonstrated that the majority of the blood pressure-lowering effect in all groups was seen by Week 2, with a plateau being reached by Week 4.

The proportion of patients achieving their blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) was 8.8% on placebo, 20.0 – 36.3% on monotherapy, and 35.0 – 53.2% on combination therapy. A statistical comparison of each combination with its respective components showed significant superiority of combination therapy in achieving goal blood pressure (Table 7).

Table 7: Study CS8663-A-U301 - Number (%) of patients achieving their blood pressure goal at Week 8 (FAS, LOCF)

OM/AML (mg)	**N**	**N (%) At goal**	**Single Component (mg)**	**N**	**N (%) At goal**	**p-value**	**Adjusted p-value**
10/5	163	57 (35.0%)	OM 10	160	32 (20.0%)	0.0009	0.0045
			AML 5	161	34 (21.1%)	0.0023	
20/5	160	68 (42.5%)	OM 20	159	42 (26.4%)	0.0009	0.0035
			AML 5	161	34 (21.1%)	<0.0001	
40/5	157	80 (51.0%)	OM 40	160	58 (36.3%)	0.0045	0.0045
			AML 5	161	34 (21.1%)	<0.0001	
10/10	161	79 (49.1%)	OM 10	160	32 (20.0%)	<0.0001	0.0044
			AML 10	163	53 (32.5%)	<0.0012	
20/10	158	84 (53.2%)	OM 20	159	42 (26.4%)	<0.0001	0.0002
			AML 10	163	53 (32.5%)	<0.0001	
40/10	161	79 (49.1%)	OM 40	160	58 (36.3%)	0.0033	0.0045
			AML 10	163	53 (32.5%)	0.0004	

A post hoc analysis of the proportions of patients achieving normalised blood pressure (that is, SeDBP < 90 mmHg) again confirmed that treatment response was better on OM/AML combination therapy than on either component at corresponding doses.

Titration Effect

The 8-week double-blind period of study 301 (Period II) was followed by a 44-week open-label period (Period III) in which all patients initially received OM/AML 40/5 mg. A post hoc analysis evaluated the effect on blood pressure of switching to OM/AML 40/5 mg in patients who were not at their blood pressure goal (non-responders) following 8 weeks of double-blind treatment with OM 40 mg alone, AML 5 mg alone or OM/AML 20/5 mg. At the time of the switch from Period II to Period III, the investigators remained blinded to the previous Period II dose. After 2 weeks of treatment with OM/AML 40/5 mg, the additional mean changes in SeSBP/SeDBP observed were:

- -13.4/-8.4 mmHg for non-responders previously randomised to OM 40 mg,
- -9.1/-5.2 mmHg for non-responders previously randomised to AML 5 mg, and
- -3.9/-3.0 mmHg for non-responders previously randomised to OM/AML 20/5 mg.

Changes in Inflammatory Markers from Baseline to Week 8 with LOCF

Changes in inflammatory markers from baseline to Week 8 with LOCF were analysed for the following select treatment groups: placebo, OM 40 mg, AML 10 mg, OM 20 mg + AML 5 mg, and OM 40 mg + AML 10 mg. Across the select treatment groups, there was no consistent pattern to the change in hsCRP that would indicate a treatment effect. Similar observations were made regarding the analysis results for mean change and mean percent change in metalloproteases 2, metalloproteases 9, tPA, PAI-1, and microalbuminuria from baseline to Week 8 with LOCF.

Trough to Peak Blood Pressure Analysis

A total of 573 patients with mild to severe hypertension enrolled in the pharmacokinetic sub-study. Sampling times were chosen to correspond with the time of the trough steady-state concentration (that is, pre-dose) and the approximate time range of maximum concentrations (C_{max}) for each of the drugs. Pharmacokinetic samples were obtained at the Week 8 visit: pre-dose (trough) samples were obtained for both olmesartan and amlodipine; two samples were taken at 0.5 to 2 hours post-dose for olmesartan; and two samples were taken at 4 to 10 hours post-dose for amlodipine. Each pharmacokinetic sampling was preceded by blood pressure measurements. Blood pressure was measured at trough prior to administration of the dose for the day. Blood pressure was measured at peak at 0.5 to 2 hours and 4 to 10 hours post dose to administration of the dose for the day. Patients were seated for 5 minutes prior to the measurement. Two additional measurements were taken at one minute intervals thereafter. Blood pressure was measured at approximately the same time of day across different visits in order to minimise any effects of a diurnal rhythm when comparing on-dose measurements to baseline measurements.

A total of 531 patients had valid blood pressure measurements. Trough-to-peak ratio for a patient was calculated as the Week 8 trough change from baseline divided by the maximum reduction in blood pressure selected from the following measurements:

Week 8 trough change-from-baseline,
Week 8 at 0.5-2 hour change-from-baseline, and
Week 8 at 4-10 hour change-from-baseline.

The ratio was considered missing when the sign of the trough measurement was different from the sign of the peak measurement.

These results indicate that approximately 70% to 80% of the maximum blood pressure reduction effect at peak was maintained at trough for all active treatment arms.

Subgroup analyses

Sub-group analyses were conducted for study 301. It was not specifically specified whether these were analysed post-hoc or were pre-defined. The principal subgroup analyses evaluated the effects of age, gender and hypertension severity on the efficacy of double-blind treatment with OM/AML combination therapy. Subgroup analyses of study 301 also evaluated the effects of diabetic status, race and ethnicity on efficacy.

Additional sub-group analyses by prior antihypertensive medication use (that is, naïve or non-naïve patients) and by body mass index (BMI $\geq$ 30 kg/m^2 and < 30 kg/m^2) were also performed for study 301 only.

Some expected outcomes were observed in certain sub-group analyses. The proportions of diabetic patients achieving BP goal were lower than for non-diabetic patients, largely because of the more stringent target BP for the diabetic sub-group (< 130/80 mmHg) than for the non-diabetic sub-group (< 140/90 mmHg). Other differences between sub-groups were generally minor and inconsistent. In all subgroups, OM/AML combination therapy was numerically more effective than either monotherapy at corresponding doses. BP trends were similar between sub-groups and there were no findings which suggested a requirement for dose adjustment in any sub-group.

There were no analyses in relation to isolated systolic hypertension.

Comment

The clinical program for OM/AML was designed to meet the requirements of the TGA-adopted EU guideline on fixed combination products and the TGA-adopted EU guideline on the clinical investigation of antihypertensive medicinal products, including fixed antihypertensive combinations.[5,6]

These guidelines require:

(i) data on the potential for pharmacokinetic (PK) interaction between the two components

(ii) dose-response data preferably from a factorial design study

(iii) evidence that both components contribute to the efficacy of the combination, with superior efficacy of the combination relative to each component

(iv) data relating to use of add-on therapy with the second drug in non-responders to the first drug and

(v) long-term safety data in at least 300 – 600 patients for 6 months or longer.

The requirements for pharmacokinetic data were met by data presented above in this evaluation report. The study design of study 301 was appropriate to assess efficacy of OM/AML combination therapy compared to the efficacy of each monotherapy. The design allowed assessment of the contribution of each component of the combination.

In order to obtain a marketing authorisation for a fixed combination, it is mandatory to prove that each active component in the scheduled dosage independently contributes towards the positive evaluation of the combination drug. Dose-finding studies are necessary for identifying the appropriate dosages of the components of a fixed combination. Preferentially, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their

[6] EMEA, Committee for Medicinal Products for Human Use (CHMP), 23 June 2004. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev 2.

respective components and with placebo. Ascending dosages (for example, in a range of dose equal or superior to two) of the fixed combination could be tested in patients with insufficient response.

It is important that the clinical studies should be designed in accordance with the proposed indication. It is mandatory that at least one or two pivotal clinical study/-ies is/are performed in a population of patients whose blood pressure cannot be normalised with one or all of the mono-components.

Guidelines suggest that it is necessary (but not sufficient) that the results of a valid clinical trial evaluating a fixed low-dose combination document show a statistically significant and clinically relevant greater blood pressure lowering effect (for example, >2 mmHg with respect to SeDBP) than placebo, whereas the difference to each component (same sub-therapeutic low dose as in the fixed combination) given separately has to be at least statistically significant. In addition, the response rate on the low-dose fixed combination should exceed that on placebo by an amount which is statistically significant and clinically valuable.

Study 301 showed that combinations of OM and AML at each dose level reduced mean SeDBP and SeSBP to a statistically significant and clinically relevant extent compared with each respective monotherapy component. The proportions of patients reaching BP goal and the proportions of patients with normalised BP were greater in the OM/AML combination dose groups than in the corresponding monotherapy groups. The BP response was dose-related, with the greatest mean reductions in BP and the greatest response rates being observed at the highest combination dose (OM/AML 40/10 mg).

With the four proposed dose combinations of OM + AML, mean DBP reductions in study 301 ranged from 14.0 mmHg to 19.0 mmHg; mean SBP reductions ranged from 23.6 mmHg to 30.1 mmHg. The additional lowering of DBP (4.4 mmHg to 8.5 mmHg) and SBP (8.3 mmHg to 15.4 mmHg) achieved with the OM + AML combination therapies compared to the component monotherapies are clearly in a range that is considered clinically meaningful, and it was realised after only 2 weeks of treatment.

At Week 2 of study 301, with the four proposed dose combinations of OM + AML, mean DBP reductions ranged from 12.9 mmHg to 17.4 mmHg; mean SBP reductions ranged from 22.1 mmHg to 27.5 mmHg. The percentage of patients who reached their blood pressure goal at Week 2 ranged from 31.8 % to 50.0 % for the groups treated with the four proposed dose combinations and 14.3 % to 31.2 % for the groups treated with the corresponding monotherapies. The combination of OM + AML reduces blood pressures into a range that is associated with improved cardiovascular outcomes. Furthermore, the shorter time frame of blood pressure reduction brought about by the use of a combination regimen as initial therapy can be of major clinical relevance.

The lowest proposed dose combination (OM 20 mg + AML 5 mg) produces a larger blood pressure reduction than the highest doses of monotherapy (OM 40 mg or AML 10 mg) and therefore is an appropriate starting dose combination. With the larger blood pressure reduction achieved with OM 20 mg + AML 5 mg combination therapy, more patients reach their blood pressure goal than on the corresponding monotherapies (OM 20 mg or AML 5 mg) or even on the highest doses of the monotherapies (OM 40 mg or AML 10 mg).

Overall the results support the proposed indication for use as first-line therapy for the treatment of hypertension.

Study CS8663-A-E302

Study Design and Objectives

This was a multicentre, multi-national, randomised, double-blind, parallel-group trial consisting of a 1- to 2-week taper-off phase (applicable to eligible patients being treated with antihypertensive

medication other than OM 20 mg or OM 40 mg at the time of screening for the trial) and two treatment periods (Period I and Period II).

Period I (Visit 2 and Visit 3; Day 1 to Week 8) was an 8-week open-label period during which all patients received monotherapy with OM 20 mg. At the end of Period I (Visit 4/Week 8 [randomisation visit]), only non-responders were eligible to be randomised and enter Period II. Patients whose BP was controlled on OM 20 mg at Week 8 were discontinued from the study.

Period II (Visit 4, Visit 5, and Visit 6; Week 8 to Week 16) was an 8-week double-blind period during which patients non-responsive to OM 20 mg treatment during Period I were assigned randomly in a 1:1:1 ratio to one of three treatment groups: OM 20 mg + placebo, OM 20 mg + AML 5 mg, or OM 20 mg + AML 10 mg.

Patients recruited to participate in the trial had a history of moderate to severe hypertension or were patients with newly diagnosed moderate to severe hypertension. Patients with a history of hypertension were further classified by type of prior antihypertensive treatment (that is, treated with OM therapy [20 mg or 40 mg] or treated with antihypertensive medications other than OM, most commonly ACE inhibitors).

Primary Objective: The primary objective was to demonstrate the additional antihypertensive efficacy in lowering trough sitting diastolic blood pressure (DBP) gained by adding amlodipine 5 mg or 10 mg to the treatment regimen in patients with hypertension not adequately controlled on olmesartan medoxomil 20 mg alone as assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment.

Secondary Objectives: These were:

- To evaluate after 4 weeks and 8 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting systolic blood pressure (SBP) lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate after 4 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting DBP lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate the additional antihypertensive efficacy in DBP and SBP lowering using 24-hour ambulatory blood pressure monitoring (ABPM) after 8 weeks of double-blind treatment;
- To evaluate the number and percentage of patients in each treatment group achieving BP goal (defined as BP <140/90 mmHg, <130/80 mmHg for diabetic patients) as assessed by conventional BP measurements after 4 weeks and after 8 weeks of double-blind treatment; and
- To evaluate the safety and tolerability of the co-administration of OM and AML versus monotherapy with OM 20 mg after 8 weeks of double-blind treatment.

Statistical Methods

The statistical analysis of the primary efficacy parameter was performed on the Full Analysis Set (Intent-to-Treat approach) using the LOCF approach for missing data. The primary analysis was repeated for the Full Analysis Set using the observed case (OC) approach and for the Per-Protocol Set (using OC). Analysis of the primary efficacy parameter was performed using an Analysis of Covariance (ANCOVA) model with treatment and pooled centre as effects and baseline DBP as a covariate. Comparisons of the combination therapies (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) versus monotherapy (OM 20 mg + placebo) were made using Dunnett's test to ensure an overall Type I error of 5%.

Analyses for the secondary efficacy parameters were conducted using the statistical model as described above on the Full Analysis Set (LOCF), with supportive analyses utilising the Full

Analysis Set (OC) and the Per-Protocol Set. The secondary efficacy parameters concerning the 24-hour ABPM and the conventional BP measurements were analysed using the same ANCOVA model as used for the confirmatory analysis. Analysis of the number and percentage of patients reaching BP goal after 4 and 8 weeks of double-blind treatment was accomplished by means of the Cochran-Mantel-Haenszel test stratified by trial centre. Pooling was applied to small centres randomising a small number of patients (<10 patients).

Multiplicity

In the ANCOVA model, the hypotheses listed above were tested using Dunnett's test to ensure an overall Type I error of 5% with corresponding 95% 2-sided confidence intervals presented. For the secondary efficacy parameters except percentage of patients achieving BP goal, adjustment for multiple testing was made per parameter using Dunnett's test, as for the primary efficacy analysis. However, adjustment for multiplicity was not made across parameters or across analysis sets.

Inclusion and Exclusion Criteria

Patients enrolled in this study included males and females ≥18 years of age, with a history of moderate to severe hypertension (SBP ≥160 mmHg and DBP ≥100 mmHg). At the screening visit, newly diagnosed hypertensive patients were required to have a mean sitting BP of ≥160/100 mmHg. There were no specific BP requirements at this visit for patients who were required to taper-off their antihypertensive medication (other than OM 20 or 40 mg). Patients being treated with either OM 20 mg or OM 40 mg had to have a previous diagnosis of moderate to severe hypertension and were required to have a mean sitting BP of ≥140/90 mmHg.

The BP requirements for entering the open-label monotherapy treatment period at Visit 2 included a mean sitting BP of ≥160/100 mmHg, a mean 24-hour DBP of ≥ 84 mmHg, and at least 30% of daytime DBP readings >90 mmHg. Patients treated with either OM 20 mg or OM 40 mg at the beginning of the trial had to have a mean sitting BP of ≥140/90 mmHg, a mean 24-hour DBP of ≥80 mmHg, and at least 30% of daytime DBP readings >85 mmHg.

To enter the double-blind treatment period at Visit 4, patients needed to be non-responders to OM 20 mg. A non-responder was defined as mean trough sitting DBP ≥90 mmHg; mean trough sitting SBP ≥140 mmHg; and mean 24-hour DBP ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg.

Study Population

In total, 722 patients entered the monotherapy baseline period (Period I). Of these, 538 patients (263 men, 275 women; mean age 56.8 years, range 19 – 80 years) were randomised to double-blind treatment (Period II). The randomised treatment groups were comparable with respect to demographic and baseline characteristics. The majority of the randomised patients (525; 97.6%) completed the study as intended.

Efficacy Results

Changes in Blood Pressure from Baseline

In study 302, patients whose BP was not adequately controlled after 8 weeks of OM 20 mg monotherapy (Period I) received add-on AML 0, 5 or 10 mg in the randomised double-blind Period II. Both active doses of add-on AML provided a statistically significant additional BP-lowering effect compared with add-on placebo (Table 8). The effect is likely to be clinically relevant. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with OM 20 mg + placebo therapy: -2.7 mmHg for OM 20 mg + AML 5 mg (p=0.0006) and -3.2 mmHg for OM 20 mg + AML 10 mg (p<0.0001).

For mean sitting SBP, the adjusted mean change from baseline (Week 8) to Week 16 with LOCF was -10.2 mmHg for the OM 20 mg + placebo treatment group, -16.1 mmHg for the OM 20 mg +

AML 5 mg treatment group, and -16.7 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting SBP from baseline (Week 8) to Week 16 with LOCF when compared with OM 20 mg + placebo therapy: -5.8 mmHg for OM 20 mg + AML 5 mg ($p<0.0001$) and -6.4 mmHg for OM 20 mg + AML 10 mg ($p<0.0001$).

The adjusted mean change from baseline (Week 8) to Week 16 in 24-hour mean DBP was -4.5 mmHg for the OM 20 mg + placebo treatment group, -7.3 mmHg for the OM 20 mg + AML 5 mg treatment group, and -8.4 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in 24-hour adjusted mean DBP from baseline (Week 8) to Week 16 LOCF when compared with OM 20 mg + placebo therapy: -2.8 mmHg for OM 20 mg + AML 5 mg ($p=0.0031$) and -3.9 mmHg for OM 20 mg + AML 10 mg ($p<0.0001$).

Table 8: Study CS8663-A-E302 - Mean (SD) change (mmHg) from baseline (Week8 [a]) to Week 16 (after 8 weeks of double-blind therapy) in BP variables (FAS, LOCF)

	OM 20 mg/placebo (N=179)	**OM/AML 20/5 mg (N=182)**	**OM/AML 20/10 mg (N=177)**
SeDBP (primary endpoint)			
Mean change (SD)	-7.8 (7.86)	-10.6 (7.20)	-11.1 (8.01)
Mean difference (SE)	-	-2.7 (0.75)	-3.2 (0.76)
95% CI	-	-4.4, -1.1	-4.9, -1.5
p-value	-	0.0006	<0.0001
SeSDP (secondary endpoint)			
Mean change (SD)	-10.6 (12.89)	-16.2 (10.66)	-16.5 (12.93)
Mean difference (SE)	-	-5.8 (1.18)	-6.4 (1.18)
95% CI	-	-8.4, -3.2	-9.1, -3.8
p-value	-	<0.0001	<0.0001

[a] end of the OM 20mg monotherapy run-in period

The results for mean 24-hour, daytime and night-time BP values (by ambulatory blood pressure monitoring [ABPM]) showed similar trends to those for conventional BP measurements. The ABPM data confirmed that the effect of OM/AML combination therapy was maintained over the 24-hour dose interval.

After 4 weeks of treatment (Week 12), the adjusted mean change in sitting DBP from baseline was -6.4 mmHg for the OM 20 mg + placebo treatment group, -7.2 mmHg for the OM 20 mg + AML 5 mg treatment group, and -9.1 mmHg for the OM 20 mg + AML 10 mg treatment group. After 8 weeks of treatment (Week 16) without LOCF for the Full Analysis Set, the adjusted mean change was -7.9 mmHg for the OM 20 mg + placebo treatment group, -10.6 mmHg for the OM 20 mg + AML 5 mg treatment group, and -10.9 mmHg for the OM 20 mg + AML 10 mg treatment group. After 4 weeks of double-blind therapy (Week 12), the reduction in the adjusted mean sitting DBP was numerically greater in the OM 20 mg + AML 10 mg treatment group compared to the OM 20 mg + AML 5 mg treatment group.

A similar analysis for sitting SBP from baseline (Week 8) to Week 12, Week 16 without LOCF, and Week 16 with LOCF for the Full Analysis Set showed that mean baseline (Week 8) sitting SBP values were similar for the 3 treatment groups. The adjusted mean change from baseline (Week 8) to Week 16 with LOCF was -10.2 mmHg for the OM 20 mg + placebo treatment group, -16.1 mmHg for the OM 20 mg + AML 5 mg treatment group, and -16.7 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in

statistically significant reductions in sitting SBP when compared with OM 20 mg + placebo therapy: -5.8 mmHg for OM 20 mg + AML 5 mg (p<0.0001) and -6.4 mmHg for the OM 20 mg + AML 10 mg group (p<0.0001).

After 4 weeks of treatment (Week 12), the adjusted mean change was -9.0 mmHg for the OM 20 mg + placebo treatment group, -11.8 mmHg for the OM 20 mg + AML 5 mg treatment group, and -15.3 mmHg for the OM 20 mg + AML 10 mg treatment group. The differences from OM 20 mg + placebo in adjusted mean change for both the OM 20 mg + AML 5 mg treatment group (-2.9 mmHg; p=0.0220) and the OM 20 mg + AML 10 mg treatment group (-6.3 mmHg; p<0.0001) were statistically significant. At this time point, the reduction in the adjusted mean sitting SBP was 3.5 mmHg greater in the OM 20 mg + AML 10 mg treatment group compared to the OM 20 mg + AML 5 mg treatment group.

Percentage of Patients Who Reached Their blood pressure goal

The proportions of patients reaching BP goal (< 140/90 mmHg for non-diabetic patients; < 130/80 mmHg for diabetic patients) were significantly greater in the add-on AML groups than in the add-on placebo group and were similar for the two active combination groups as summarised in Table 9. A post hoc analysis of patients achieving normalised BP confirmed that treatment response was better on OM/AML combination therapy than on OM/placebo therapy.

Table 9: Study CS8663-A-E302 - Number (%) of patients achieving BP goal or normalised BP at Week 16 (FAS, LOCF)

	OM 20 mg/placebo (N=179)	**OM/AML 20/5 mg (N=182)**	**OM/AML 20/10 mg (N=177)**
N (%) achieving BP goal	51 (28.5%)	81 (44.5%)	81 (45.8%)
N (%) achieving normalised BP	88 (49.2%)	117 (64.3%)	121 (68.4%)

The greater reductions in BP observed with OM and AML combination treatment translated into significantly more patients achieving pre-defined BP goals in both OM + AML combination treatment groups compared to the OM 20 mg + placebo treatment group. Compared to patients treated with OM 20 mg + placebo (28.5% achieving goal), the percentage of patients achieving BP goal at Week 16 with LOCF was significantly higher in the OM 20 mg + AML 5 mg treatment group (44.5%; p=0.0011) and in the OM 20 mg + AML 10 mg treatment group (45.8%; p=0.0004).

Mean changes in daytime, night-time, and 24-hour mean diastolic blood pressure and systolic blood pressure from baseline (Week 8) to Week 16 without LOCF using ambulatory blood pressure monitoring

Analysis of the results for mean changes in 24-hour, daytime, and night-time mean DBP and SBP, respectively, from baseline (Week 8) to Week 16 by treatment group showed the following:

The adjusted mean change from baseline (Week 8) to Week 16 in 24-hour mean DBP was -4.5 mmHg for the OM 20 mg + placebo treatment group, -7.3 mmHg for the OM 20 mg + AML 5 mg treatment group, and -8.4 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in 24-hour mean DBP when compared with OM 20 mg + placebo therapy: -2.8 mmHg for OM 20 mg + AML 5 mg (p=0.0031) and -3.9 mmHg for OM 20 mg + AML 10 mg (p<0.0001).

The adjusted mean change from baseline (Week 8) to Week 16 in 24-hour mean SBP was -6.5 mmHg for the OM 20 mg + placebo treatment group, -11.4 mmHg for the OM 20 mg + AML 5 mg treatment group, and -12.4 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in 24-hour

mean SBP when compared with OM 20 mg + placebo therapy: -4.9 mmHg for OM 20 mg + AML 5 mg (p=0.0020) and -5.8 mmHg for the OM 20 mg + AML 10 mg (p=0.0003).

Results were similar for mean changes in daytime mean DBP and SBP and night-time mean DBP and SBP.

Analysis of ABPM parameters for the Per-Protocol population at Week 16 yielded similar results as the Full Analysis Set.

Subgroup analyses

In the subgroup analyses, the efficacy of the OM + AML combination treatment regimens compared to OM 20 mg + placebo was similar for all age groups, for both males and females, and for all categories of hypertension severity.

Comment

Overall, study 302 demonstrated a statistically significant and clinically relevant benefit of add-on AML compared with add-on placebo in patients whose blood pressure was not adequately controlled by 8 weeks of monotherapy with OM 20 mg. The proportions of patients reaching their blood pressure goal (< 140/90 mmHg for non-diabetic patients; < 130/80 mmHg for diabetics) and the proportions of patients with normalised blood pressure were greater on combination therapy than on continued monotherapy. These results support the proposed use of the OM/AML 20/5 mg fixed-dose combination in OM 20 mg monotherapy non-responders.

Study CS8663-A-U303

Study Design and Objectives

This was a 52-week, Phase III, randomised, parallel-group, multicentre, multi-national trial consisting of 4 periods: Period I, an 8-week, open-label treatment period with AML 5 mg monotherapy; Period II, an 8-week, double-blind treatment period with randomisation to a fixed combination of OM and AML; Period III, an 8-week, double-blind treatment period with dose up-titration if needed; and Period IV, a 28-week, open-label, long-term extension period with possible dose titration.

The design of study 303 is shown in Figure 2. After 1 to 2 weeks of tapering off previous antihypertensive medication (not applicable for newly diagnosed hypertensive patients or patients who were on AML 5 mg or 10 mg), patients eligible for the study entered an 8- week, open-label, run-in period with AML 5 mg (Period I). Patients who were on AML 5 mg or 10 mg at screening entered directly into Period I with AML 5 mg without tapering off antihypertensive medication.

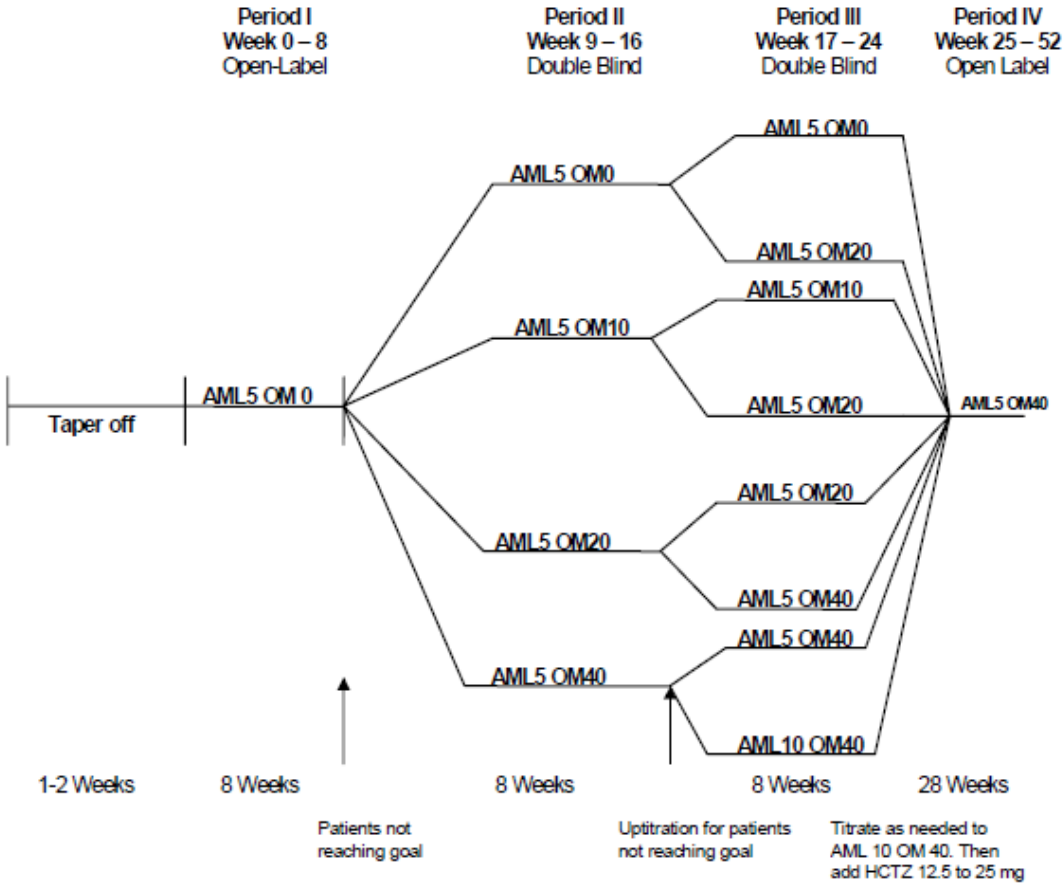
At the end of Period I, patients who did not respond adequately to AML 5 mg monotherapy (that is, non-responders, defined as patients with a mean sitting trough DBP ≥90 mmHg, a mean sitting trough SBP ≥140 mmHg, and a mean 24-hour DBP assessed by ABPM of ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg) were assigned randomly to double-blind treatment for 8 weeks (Period II) with OM 10 mg, 20 mg, 40 mg, or placebo in addition to AML 5 mg. Patients with a mean sitting trough DBP >115 mmHg or a mean sitting trough SBP >200 mmHg were excluded from further participation. Patients who responded adequately to AML 5 mg monotherapy were discontinued from the study.

At the end of Period II, patients whose BP was not adequately controlled (defined as a mean sitting trough DBP ≥90 mmHg and a mean sitting trough SBP ≥140 mmHg) underwent dose titration during Period III. Patients randomised to combination therapy with OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, and OM 40 mg + AML 5 mg had their doses titrated to OM 20 mg + AML 5 mg, OM 40 mg + AML 5 mg, and OM 40 mg + AML 10 mg, respectively. Patients randomised to therapy with placebo + AML 5 mg had their dose titrated to OM 20 mg + AML 5 mg. Patients whose BP was adequately controlled at the end of Period II remained on the same randomised

treatment during Period III. Patients and investigators remained blinded to study medication during Period III.

At the end of Period III, patients entered a 28-week, open-label, long-term extension period (Period IV). All patients initially received open-label OM 40 mg + AML 5 mg. If BP was inadequately controlled at this dose (defined as a mean sitting trough DBP ≥90 mmHg and a mean sitting trough SBP ≥140 mmHg), investigators could titrate the doses first to OM 40 mg + AML 10 mg and then to triple therapy with OM 40 mg + AML 10 mg + hydrochlorothiazide (HCT) 12.5 mg and if needed to OM 40 mg + AML 10 mg + HCT 25 mg.

Figure 2: Study CS8663-A-U303 – Study design



The primary objective was to demonstrate the additional antihypertensive efficacy in lowering sitting diastolic blood pressure (DBP) gained by adding olmesartan medoxomil 10 mg, 20 mg, or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on amlodipine 5 mg alone assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment.

Secondary objectives included the following:

- To evaluate after 4 and 8 weeks of double-blind treatment the additional antihypertensive efficacy of various combinations of OM and AML compared to the monotherapy with AML 5 mg alone in lowering sitting trough systolic blood pressure (SBP) using conventional BP measurements;
- To evaluate after 4 weeks of double-blind treatment the additional antihypertensive efficacy of various combinations of OM and AML compared to the monotherapy with AML 5 mg alone in lowering sitting trough DBP using conventional BP measurements;

- To evaluate after 8 weeks of double-blind treatment the additional antihypertensive efficacy in lowering DBP and SBP using 24-hour ambulatory blood pressure monitoring (ABPM);
- To evaluate the effect of titration to various dose combinations of OM and AML on DBP and SBP using conventional BP measurements and 24-hour ABPM;
- To evaluate the number (%) of patients in each treatment group achieving BP goal (DBP <90 mmHg and SBP <140 mmHg for non-diabetic patients; DBP <80 mmHg and SBP <130 mmHg for diabetic patients) after 8 weeks of double-blind treatment and after the additional 8-week up-titration period as assessed by conventional BP measurements;
- To evaluate the safety and tolerability of various combinations of OM and AML versus AML 5 mg monotherapy after 8 weeks of double-blind treatment and after the additional 8-week up-titration period; and
- To evaluate the long-term safety and sustained efficacy of various combinations of OM and AML.

Statistical Methods

The primary null hypothesis was that there was no difference between OM + AML combination therapies (OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, and OM 40 mg + AML 5 mg) and placebo + AML 5 mg therapy in lowering mean trough sitting DBP after 8 weeks of double-blind treatment (Period II). A parametric Analysis of Covariance (ANCOVA) model with treatment and centre as effects and baseline mean DBP as a covariate was used to evaluate the treatment effect under this null hypothesis. The primary efficacy parameter was evaluated at the 0.05 significance level. Comparisons of the combination therapies with placebo + AML 5 mg therapy were made using Dunnett's test to ensure an overall type I error rate of 0.05.

The secondary efficacy parameters for Period II were analysed by using the same ANCOVA model as used for the primary analysis on the Full Analysis Set 1.

The numbers and percentages of patients in each treatment group who achieved BP goal during Periods II, III, and IV were tabulated. The Cochran-Mantel-Haenszel test with stratification by centre was used to compare percentages during Period II for OM + AML combination therapies and placebo + AML 5 mg therapy.

Inclusion and Exclusion Criteria

Patients enrolled in this study were male and female patients ≥18 years of age, with moderate to severe hypertension. To enter Period I, newly diagnosed hypertensive patients and patients previously on antihypertensive medications other than AML 5 mg or 10 mg must have had a mean sitting DBP ≥100 mmHg, a mean sitting SBP ≥160 mmHg, and a mean 24-hour DBP assessed by 24-hour ABPM of ≥84 mmHg with at least 30% of daytime DBP readings >90 mmHg.

To enter Period I, patients on AML 5 mg or 10 mg monotherapy must have had a mean sitting DBP ≥90 mmHg, a mean sitting SBP ≥140 mmHg, and a mean 24-hour DBP assessed by 24-hour ABPM of ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg. To be randomised to double-blind combination therapy and enter Period II, patients must have had a mean sitting trough DBP ≥90 mmHg, a mean sitting trough SBP ≥ 140 mmHg, and a mean 24-hour DBP ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg.

Study Population

In total, 1017 patients with moderate to severe hypertension entered the monotherapy baseline period (Period I). Of these, 755 patients (461 men, 294 women; mean age 55.8 years, range 28 – 80 years) were randomised to double-blind treatment in Period II. The majority of randomised patients (93.5%) completed Period II as intended. The randomised treatment groups were comparable with regard to demographic and baseline characteristics. The FAS comprised 746 patients (98.8% of those randomised) and the PP set comprised 697 patients (92.3% of those randomised).

In total, 706 patients continued into Period III of the study. In Period III, the FAS comprised 705 patients (99.9% of the total) and the PP set comprised 643 patients (91.1% of the total).

Efficacy Results

Changes in Blood Pressure From Baseline

In study 303 (Period II), OM 0, 10, 20 or 40 mg was added in a randomised double-blind manner in patients whose BP was not adequately controlled after 8 weeks on AML 5 mg monotherapy. As shown in Table 10 all active doses of add-on OM provided a statistically significant and clinically relevant additional BP-lowering effect compared with add-on placebo. Study 303 was not powered for statistical comparisons between the active treatment groups; however the benefit was numerically greater for add-on OM 20 mg and OM 40 mg than for add-on OM 10 mg.

Compared with placebo + AML 5 mg, treatment with OM + AML resulted in statistically significant reductions in sitting DBP (2.0 mmHg, p=0.0207 for OM 10 mg + AML 5 mg; 3.7 mmHg, p<0.0001 for OM 20 mg + AML 5 mg; and 3.8 mmHg, p<0.0001 for OM 40 mg + AML 5 mg).

Treatment with OM + AML (all evaluated dose regimens) demonstrated statistically significantly larger mean reductions in sitting DBP than placebo + AML 5 mg treatment at both the Week 12 and Week 16 time points. The DBP-lowering effect of OM 40 mg + AML 5 mg treatment was realised earlier than that of OM 20 mg + AML 5 mg treatment. At Week 16, the 2 highest dose regimens (OM 20 mg + AML 5 mg and OM 40 mg + AML 5 mg) demonstrated numerically larger mean reductions in sitting DBP than OM 10 mg + AML 5 mg.

Compared with placebo + AML 5 mg, treatment with OM + AML resulted in statistically significant reductions in sitting SBP (3.5 mmHg, p=0.0103 for OM 10 mg + AML 5 mg; 5.8 mmHg, p<0.0001 for OM 20 mg + AML 5 mg; and 7.1 mmHg, p<0.0001 for OM 40 mg + AML 5 mg).

Table 10: Study CS8663-A-U303 - Mean (SD) change (mmHg) from baseline (Week 8 to Week 16 (after 8 weeks of double-blind therapy) in BP variables (FAS, LOCF)

	Placebo/AML 5 mg (N=184)	**OM/AML 10/5 mg (N=189)**	**OM/AML 20/5 mg (N=187)**	**OM/AML 40/5 mg (N=186)**
SeDBP (primary endpoint)				
Mean change (SD)	-5.7 (7.66)	-7.4 (7.14)	-9.3 (7.74)	-9.5 (6.64)
Mean difference (SE)	-	-2.0 (0.73)	-3.7 (0.73)	-3.8 (0.73)
95% CI	-	-3.7, -0.2	-5.4, -2.0	-5.5, -2.1
p-value	-	0.0207	<0.0001	<0.0001
SeSDP (secondary endpoint)				
Mean change (SD)	-9.9 (12.43)	-13.1 (11.64)	-15.3 (13.32)	-16.7 (12.00)
Mean difference (SE)	-	-3.5 (1.21)	-5.8 (1.22)	-7.1 (1.22)
95% CI	-	-6.4, -0.7	-8.6, -2.9	-10.0, -4.3
p-value	-	0.0103	<0.0001	<0.0001

Mean changes in ambulatory blood pressure during Period II

The results for mean 24-hour, daytime and night-time BP values (by ABPM) were similar to those for conventional BP measurements. The ABPM data also confirmed that the effect of OM + AML combination therapy was maintained over the 24-hour dose interval.

Percentage of Patients Who Reached Their blood pressure goal

The proportions of patients reaching BP goal (< 140/90 mmHg for non-diabetic patients; < 130/80 mmHg for diabetic patients) were significantly greater in the add-on OM groups than in the add-on placebo group and were numerically greater for add-on OM 20 or 40 mg than for add-on OM 10 mg (Table 11).

Table 11: Study CS8663-A-U303 – Number (%) of patients achieving BP goal or normalised BP at Week 16 in Period II of study 303 (FAS, LOCF)

	Placebo/AML 5 mg (N=184)	**OM/AML 10/5 mg (N=189)**	**OM/AML 20/5 mg (N=187)**	**OM/AML 40/5 mg (N=186)**
N (%) achieving BP goal	55 (29.9%)	74 (39.2%)	100 (53.5%)	94 (50.5%)
N (%) achieving normalised BP	66 (35.9%)	96 (50.8%)	116 (62.0%)	120 (64.5%)

A post hoc analysis of the proportions of patients achieving normalised BP confirmed that treatment response was better on OM + AML combination therapy than on placebo/AML therapy.

Subgroup analyses

The BP-lowering effects of OM + AML treatment during Period II were similar for the age subgroups, gender subgroups, and hypertension severity subgroups.

Results - Period III and Period IV

For patients who remained on their randomised treatment regimen during Period III, the proportion who reached BP goal at Week 24 with LOCF was higher with OM + AML treatment than with placebo + AML 5 mg treatment. For patients whose dose regimen was titrated, successively higher proportions reached BP goal with each increase in dose combination of OM + AML. The results for mean changes in ambulatory BP during Period III support the results for mean changes in sitting BP during Period III.

The BP-lowering effects of OM + AML treatment during Period III were similar for the age subgroups, gender subgroups, and hypertension severity subgroups.

In total, 692 patients entered the open-label Period IV and initially received OM 40 mg + AML 5 mg. For the 563 patients on OM 40 mg + AML 5 mg at Week 34/Early Termination, the mean sitting DBP was 83.6 mmHg and the mean sitting SBP was 132.2 mmHg. For the 121 patients on OM 40 mg + AML 10 mg at Week 34/Early Termination, the mean sitting DBP was 90.3 mmHg and the mean sitting SBP was 143.0 mmHg. For the 6 patients on OM 40 mg + AML 10 mg + HCT 12.5 mg at Week 34/Early Termination, the mean sitting DBP was 89.3 mmHg and the mean sitting SBP was 147.6 mmHg. For the 1 patient on OM 40 mg + AML 10 mg + HCT 25 mg at Week 34/Early Termination, sitting DBP was 92.0 mmHg and sitting SBP was 155.3 mmHg.

Titration from OM 40 mg + AML 5 mg to OM 40 mg + AML 10 mg during Period IV resulted in a mean reduction in sitting DBP of 5.0 mmHg and a mean reduction in sitting SBP of 8.7 mmHg. Titration from OM 40 mg + AML 10 mg to OM 40 mg + AML 10 mg + HCT 12.5 mg resulted in a mean reduction in sitting DBP of 3.7 mmHg and a mean reduction in sitting SBP of 3.1 mmHg. Of the 692 patients exposed to OM 40 mg + AML 5 mg during Period IV, 502 (72.5%) reached BP goal. Of the 127 patients exposed to OM 40 mg + AML 10 mg, 46 (36.2%) reached BP goal. Of the

6 patients exposed to OM 40 mg + AML 10 mg + HCT 12.5 mg, 2 (33.3%) reached BP goal. The one patient exposed to OM 40 mg + AML 10 mg + HCT 25 mg did not reach BP goal.

Comment

The results of the principal double-blind period of study 303 (Period II) demonstrated that add-on OM 10, 20 and 40 mg to AML 5 mg provided a statistically significant and clinically meaningful benefit compared with add-on placebo in patients whose BP was not adequately controlled by 8 weeks of monotherapy with AML 5 mg. The BP-lowering effect of add-on OM 20 mg and 40 mg was numerically superior to that of add-on OM 10 mg. Furthermore, the additional SeSBP lowering effect of the OM 40 mg dose was numerically superior to that of the OM 20 mg dose.

The proportions of patients achieving BP goal or normalised BP were greater for all add-on OM doses than for add-on placebo but were also numerically greater for add-on OM 20 mg and OM 40 mg than for add-on OM 10 mg. The optimum dose combinations for patients whose BP was not controlled by AML 5 mg alone were shown to be the OM/AML 20/5 mg and 40/5 mg combinations.

There are, however, no long term data for patients on the combination of OM/AML 20/5 or 20/10, therefore no conclusions can be drawn in relation to long term efficacy of these doses.

Dose Titration Effects

The effectiveness of combination dose titration was evaluated in Period III of study 303. Treatment in Period III remained double-blind. Additional information on the effectiveness of dose titration was derived from the open-label periods of studies 301 and 303. The double-blind period of study 301 was followed by an open-label period in which all patients switched initially to OM/AML 40/5 mg combination therapy.

Post hoc analyses have been conducted of the benefit of switching to the 40/5 mg dose in patients who had not achieved BP goal on OM 40 mg monotherapy, AML 5 mg monotherapy or OM/AML 20/5 mg combination therapy at the end of the double-blind period of study 301. Although the OM/AML 40/5 mg treatment was open-label, investigators remained blinded to the patient's prior treatment in the double-blind period. In the open-label extension periods of studies 301 and 303, dose titration from OM/AML 40/5 mg to 40/10 mg was permitted when required.

Table 12 summarises the beneficial effect of dose titration observed in the pre-planned analyses for Period III of study 303, in the pre-planned analyses of the open-label titration periods of studies 301 and 303, and in the post hoc analyses of the switch to open-label therapy in study 301.

Table 12: Mean (SD) changes in BP (mmHg) following up-titration of OM/AML dose

Dose titration step (OM/AML)	Study	N	Mean (SD) change	
			Se DBP	SeSBP
Titrations from monotherapy to OM/AML combination therapy				
0/5 mg to 20/5 mg	303 Period III	107	-8.2 (6.55)	-12.6 (11.47)
0/5 mg to 40/5 mg	301 Switch to open-label period	104	-5.2 (8.38)	-9.1 (12.99)
40/0 mg to 40/5 mg	301 Switch to open-label period	83	-8.4 (8.19)	-13.4 (13.95)
Up-titration of OM/AML combination dose				
10/5 mg to 20/5 mg	303 Period III	82	-5.6 (7.02)	-7.5 (10.42)
20/5 mg to 40/5 mg	303 Period III	58	-6.2 (7.47)	-10.6 (12.76)
	301 Switch to open-label period	71	-3.0 (8.97)	-3.9 (14.67)
40/5 mg to 40/10 mg	303 Period III	57	-8.2 (7.34)	-12.3 (11.12)
	301 open-label titration period (completed)	1096	-4.8 (7.93)	-7.3 (12.81)
	303 open-label titration period	127	-5.0 (6.85)	-8.7 (10.26)

The results in Table 12 provide supporting evidence that changing from monotherapy with AML 5 mg to combination therapy with OM/AML 20/5 mg or 40/5 mg, when needed, results in a clinically relevant further change in BP of - 5.2 to - 8.2 mmHg for SeDBP and - 9.1 to - 12.6 mmHg for SeSBP. The change from OM 40 mg to OM/AML 40/5 mg at the start of the open-label period of study 301 resulted in a further change in BP of - 13.4/- 8.4 mmHg.

The results from the double-blind up-titration period of study 303 (Period III) and the supporting data from the open-label periods of studies 301 and 303 confirm that titration of the OM/AML combination dose from 20/5 mg to 40/5 mg or from 40/5 mg to 40/10 mg, as in the proposed Australian Product Information for OM/AML, results in a substantial clinically relevant further decrease in BP.

Long-term Efficacy

The open-label extension period of study 301 (44 weeks in duration) was designed to evaluate the long-term efficacy and safety of OM/AML combination therapy. The long-term open-label period of study 303 has a planned duration of 28 weeks, with data presented for the first 10 weeks of open-label treatment. In both studies treatment was initiated at an OM/AML dose of 40/5 mg and titration of the treatment regimen was recommended.

Table 13 summarises the results for SeDBP and SeSBP over time for the pooled analysis of the two long-term periods; data beyond 10 weeks derive from study 301 only. The data show an initial decrease in BP during the first few weeks of treatment with any dose regimen. Thereafter, BP tended to stabilise. This pattern would be expected since patients not achieving target BP were up-titrated to a higher dose; however, the data do demonstrate that the efficacy of each dose regimen was maintained over the long term in patients remaining on that dose.

There are no long term data for patients on the combination of OM/AML 20/5 or 20/10, therefore no conclusions can be drawn in relation to long term efficacy of these doses.

Table 13: Mean blood pressure (mmHg) by week and dose – Integrated analysis of study 301 Period III and study 303 Period IV

	OM/AML 40/5 mg	**OM/AML 40/10 mg**	**OM/AML/HCT 40/10/12.5 mg**	**OM/AML/HCT 40/10/25 mg**
Start of open-label period				
N	2375			
SeDBP mean (SD)	87.8 (9.59)			
SeSBP mean (SD)	140.6 (17.25)			
N (%) to BP goal	1019 (42.9)			
4 weeks				
N	1549	711	32	
SeDBP mean (SD)	83.0 (7.72)	87.1 (8.23)	92.6 (7.88)	
SeSBP mean (SD)	131.4 (12.43)	141.6 (14.33)	145.8 (14.86)	
N (%) to BP goal	1112 (71.8)	254 (35.7)	1 (3.1)	
10 weeks				
N	1247	555	397	31
SeDBP mean (SD)	82.6 (7.49)	85.2 (8.09)	85.8 (8.68)	85.2 (7.37)
SeSBP mean (SD)	130.7 (11.51)	136.7 (13.27)	140.7 (15.61)	141.9 (13.93)
N (%) to BP goal	931 (74.7)	287 (51.7)	147 (37.0)	7 (22.6)
18 weeks				
N	564	391	308	232
SeDBP mean (SD)	80.9 (7.71)	82.4 (7.61)	83.6 (8.11)	85.0 (8.09)
SeSBP mean (SD)	127.7 (11.66)	131.8 (11.21)	135.0 (13.06)	141.4 (14.83)
N (%) to BP goal	450 (79.8)	271 (69.3)	167 (54.2)	68 (29.3)
26 weeks				
N	479	360	279	316
SeDBP mean (SD)	80.1 (7.62)	81.7 (7.30)	81.5 (7.65)	83.7 (8.08)
SeSBP mean (SD)	126.0 (11.11)	130.9 (10.35)	131.3 (12.50)	137.7 (12.96)
N (%) to BP goal	412 (86.0)	268 (74.4)	192 (68.8)	131 (41.5)
34 weeks				
N	431	335	258	355
SeDBP mean (SD)	79.2 (7.01)	80.5 (7.67)	80.1 (7.52)	82.5 (8.42)
SeSBP mean (SD)	124.2 (10.17)	129.1 (10.19)	127.9 (10.86)	135.2 (13.70)
N (%) to BP goal	387 (89.8)	268 (80.0)	199 (77.1)	185 (52.1)
44 weeks				
N	412	312	248	372
SeDBP mean (SD)	79.8 (7.51)	81.3 (7.56)	80.5 (8.49)	82.7 (8.38)
SeSBP mean (SD)	125.0 (11.03)	129.1 (11.20)	129.1 (11.98)	135.8 (14.07)
N (%) to BP goal	355 (86.2)	244 (78.2)	171 (69.0)	180 (48.4)

Efficacy Data Supporting Initial Therapy With Proposed Doses

The clinical program for OM/AML was designed to meet the requirements of EU guidelines on fixed antihypertensive combinations. The study design of study 301 was appropriate to assess efficacy of OM/AML combination therapy compared to the efficacy of each monotherapy. The design allowed assessment of the contribution of each component of the combination.

In order to obtain a marketing authorisation for a fixed combination, it is necessary to prove that each active component in the scheduled dosage independently contributes

It is mandatory that at least one or two pivotal clinical study/-ies is/are performed in a population of patients whose blood pressure cannot be normalised with one or all of the mono-components. Guidelines suggest that it is necessary that the results of a valid clinical trial evaluating a fixed low-dose combination document a statistically significant and clinically relevant greater blood pressure lowering effect (for example, >2 mmHg with respect to SeDBP) than placebo, whereas the difference to each component (same sub-therapeutic low dose as in the fixed combination) given separately has to be at least statistically significant. In addition, the response rate on the low-dose fixed combination should exceed that on placebo by an amount which is statistically significant and clinically valuable.

The primary efficacy analysis during Period II of study 301 demonstrated that 8 weeks of double-blind treatment with OM + AML combination therapy resulted in larger mean reductions in seated DBP than the corresponding monotherapies

Treatment with all 4 proposed dose combinations (OM 20 mg/AML 5 mg, OM 20 mg/AML 10 mg, OM 40 mg/AML 5 mg, and OM 40 mg/AML 10 mg) reduced LS mean seated DBP by an additional 4.4 mmHg to 8.5 mmHg compared with the component monotherapies. The treatment comparisons of LS mean change in seated DBP between each of the 4 proposed combination therapies and the component monotherapies were all highly statistically significant. The additional DBP lowering achieved with the combination therapies compared with the component monotherapies is in a range that is likely to be clinically meaningful.

Similar results from the analysis of change in seated SBP were observed. Treatment with the four proposed dose combinations reduced LS mean seated SBP by an additional 8.3 mmHg to 15.4 mmHg compared with the component monotherapies. The treatment comparisons of LS mean change in seated SBP between each of the 4 proposed combination therapies and the component monotherapies were all highly statistically significant.

The larger BP reductions achieved with OM + AML combination therapy translated into a comparatively higher percentage of patients on combination therapy who achieved the blood pressure goal. The percentage of patients who reached the blood pressure goal at Week 8 with LOCF ranged from 42.5 % to 53.2 % for the groups treated with the four proposed dose combinations and 21.1% to 36.3% for the groups treated with the corresponding monotherapies.

In additional analyses, across the range of observed baseline DBP values from 90 mmHg to 115 mmHg, the estimated probability of reaching DBP thresholds (< 90 mmHg and < 80 mmHg) was higher with OM 40 mg + AML 10 mg combination therapy than with OM 40 mg monotherapy or AML 10 mg monotherapy, or with OM 20 mg + AML 5 mg combination therapy. Similarly, across the range of observed baseline SBP values from 140 mmHg to 190 mmHg, the estimated probability of reaching SBP thresholds (< 140 mmHg and < 130 mmHg) was higher with OM 40 mg + AML 10 mg combination therapy than with the corresponding monotherapies, or with OM 20 mg + AML 5 mg combination therapy.

With the four proposed dose combinations of OM + AML, mean DBP reductions in study 301 ranged from 14.0 mmHg to 19.0 mmHg; mean SBP reductions ranged from 23.6 mmHg to 30.1 mmHg. The additional lowerings of DBP (4.4 mmHg to 8.5 mmHg) and SBP (8.3 mmHg to 15.4

mmHg) achieved with the OM + AML combination therapies compared to the component monotherapies are clearly in a range that is considered clinically meaningful.

At Week 2 of study 301, with the four proposed dose combinations of OM + AML, mean DBP reductions ranged from 12.9 mmHg to 17.4 mmHg; mean SBP reductions ranged from 22.1 mmHg to 27.5 mmHg. The percentage of patients who reached their blood pressure goal at Week 2 ranged from 31.8 % to 50.0 % for the groups treated with the four proposed dose combinations and 14.3 % to 31.2 % for the groups treated with the corresponding monotherapies. The combination of OM + AML reduces blood pressures into a range that is associated with improved cardiovascular outcomes. Furthermore, the shorter time frame of blood pressure reduction brought about by the use of a combination regimen as initial therapy can be of major clinical relevance.

The lowest proposed dose combination (OM 20 mg + AML 5 mg) produces a larger blood pressure reduction than the highest doses of monotherapy (OM 40 mg or AML 10 mg) and therefore is an appropriate starting dose combination. With the larger blood pressure reduction achieved with OM 20 mg + AML 5 mg combination therapy, more patients reach their blood pressure goal than on the corresponding monotherapies (OM 20 mg or AML 5 mg) or even on the highest doses of the monotherapies (OM 40 mg or AML 10 mg).

Given the abovementioned results, overall it is considered that results support the proposed indication for use as first-line therapy for the treatment of hypertension**.**

The decision on the appropriate Sevikar initial therapy dose combination for the patient will depend on the patient's baseline blood pressure and the coexistent pathologies. The lowest proposed dose combination (OM 20 mg + AML 5 mg) was shown to produce a larger blood pressure reduction than the highest doses of monotherapy (OM 40 mg or AML 10 mg) and therefore is an appropriate starting dose combination. With the larger blood pressure reduction achieved with OM 20 mg + AML 5 mg combination therapy, more patients reach their blood pressure goal than on the corresponding monotherapies (OM 20 mg or AML 5 mg) or even on the highest doses of the monotherapies (OM 40 mg or AML 10 mg).

The add-on studies 302 and 303 demonstrated that OM/AML combination therapy was statistically and clinically superior to continued monotherapy in patients whose BP was not adequately controlled by OM 20 mg alone or by AML 5 mg alone. No specific studies were conducted in which AML was added to high dose OM (40 mg) or in which OM was added to high dose AML (10 mg). However, it is reasonable to conclude that OM/AML combination therapy will be effective in patients not achieving target BP on OM 40 mg or AML 10 mg alone, based on:

- evidence that both components contribute to the efficacy of the fixed-dose combination at all dose levels (study 301), and
- evidence that addition of the second component is beneficial in patients whose BP is not adequately controlled by the first component, albeit at the lower dose of OM 20 mg (study 302) or AML 5 mg (study 303).

Justification for Second-line Therapy for Switching Patients on Any Angiotensin II Receptor Blocker (ARB), Angiotensin Converting Enzyme (ACE) Inhibitors, or Dihydropyridine Calcium Channel Blocker (CCB) Monotherapy to Sevikar

In its Clinical Overview the sponsor provided a justification for switching patients from other hypertension treatments to Sevikar. This discussion focussed on published literature comparing efficacy and safety of the various classes of anti-hypertensive agents.

In the literature olmesartan has been shown to have equal or greater efficacy compared to that of the currently available ARBs. In addition to equal or greater efficacy, there were no discernible differences between olmesartan and the other ARBs with regards to safety, which supports that patients on other ARBs could feasibly be switched to Sevikar.

Comment

Olmesartan has been shown to have equal or greater efficacy compared to that of the currently available ARBs. In addition to equal or greater efficacy, there were no discernible differences between olmesartan and the other ARBs with regards to safety. This evidence suggests that as olmesartan is equivalent to other ARBs in terms of efficacy and safety then patients on other ARBs could be switched to Sevikar. Given that ARBs may provide a better safety profile compared to ACE inhibitors there may be a case for the switching a patient on an ACE inhibitor to Sevikar. These data support a broad second-line indication.

Summary of Efficacy

The double-blind period of the factorial ***study 301*** demonstrated that OM/AML combination therapy was statistically and clinically superior to its individual components at corresponding doses in patients with mild to severe hypertension. The effects of OM/AML treatment generally increased with increasing dose of each component. In the double-blind period of study 301, BP was monitored every 2 weeks; the majority of the effect of OM/AML treatment was already present after 2 weeks.

In ***study 302***, in patients whose BP was not adequately controlled by OM 20 mg monotherapy, addition of AML 5 or 10 mg provided statistically significant and clinically relevant benefit compared with addition of placebo.

In ***study 303 (Period II)***, in patients whose BP was not adequately controlled by AML 5 mg monotherapy, addition of OM 10, 20 or 40 mg provided statistically significant and clinically relevant benefit compared with the addition of placebo. The efficacy of the add-on OM 20 mg and 40 mg doses was numerically superior to that of the add-on OM 10 mg dose. Thus the OM/AML 20/5 mg and 40/5 mg combinations provided optimal efficacy in this study.

In the controlled study periods, normalised BP (SeDBP < 90 mmHg) was achieved in 62.0 – 77.6 % of patients in OM/AML dose groups combining AML with OM 20 mg or 40 mg. Both SeSBP and SeDBP goals (< 140/90 mmHg for non-diabetic patients; < 130/80 mmHg for diabetic patients) were achieved by 42.5 – 53.5 % of patients in OM/AML dose groups combining AML with OM 20 mg or 40 mg. Titration of the OM/AML combination dose from 20/5 mg to 40/5 mg and from 40/5 mg to 40/10 mg resulted in substantial additional decreases in BP.

The results for trough-to-peak ratios in study 301, and for the ABPM data in studies 302 and 303, confirmed that the efficacy of OM/AML treatment was evident throughout the 24-hour dose interval. In addition the efficacy of OM/AML combination therapy persisted during long-term treatment, with no evidence of the development of tolerance to treatment.

Sub-group analyses of efficacy did not indicate any need for dose adjustment based on age, gender, hypertension severity, diabetic status, race or BMI.

Overall the data submitted for evaluation support approval of combination OM/AML treatment for use as first-line and second-line treatment of hypertension.

Safety

The sponsor provided an integrated analysis of tolerability and safety of OM/AML. The Phase III double-blind cohort provides information on adverse event (AE) incidences from controlled studies, while the Phase III open-label cohort provides data on long-term open-label therapy as well as data on the addition of HCTZ to the OM/AML combination. The study 301 Period II cohort was included in the safety analysis as this study included specific questioning on oedema. The Phase I cohort was included for completeness, and there were no safety signals identified from review of the Phase I cohort.

Extent of Exposure

In the Phase III double-blind cohort, a total of 2003 patients received OM/AML treatment and mean extent of exposure to OM/AML was 70.0 days (median 57 days). Exposure was considered similar for all treatment regimens.

In the Phase III open-label cohort, a total of 2376 patients received OM/AML treatment and mean extent of exposure to OM/AML was 143.6 days (median 116.6 days); 35.6 % of patients had at least 6 months OM/AML treatment. Data are also available for 742 patients who had HCTZ added to their treatment in the open-label cohort.

In the Phase III all patients cohort, 2892 patients received OM/AML dual treatment and mean extent of exposure was 166.5 days (median 115.8 days). In total, 1251 patients had at least 6 months OM/AML treatment and 173 had at least 12 months exposure.

Adverse Events

Overall Adverse Events

Phase III Double-blind Cohort

OM/AML was associated with a lower incidence of patients reporting adverse events (38.4 %) than either of its components administered as monotherapies (OM 43.4 % and AML 43.4 %) and placebo (56.8 %). In each group, the majority of adverse events were mild or moderate in severity and the distribution by maximum severity was similar across the groups. The pattern for drug-related adverse events was similar to that for all adverse events with OM/AML associated with the lowest incidences.

Phase III Open-label Cohort

The incidence of adverse events appeared to increase with increasing dose of AML from 5 to 10 mg and with the addition of HCTZ 25 mg to the combination. Once again, in each group, the majority of adverse events were mild or moderate in severity and the distribution by maximum severity was similar across the groups. The pattern for drug-related adverse events was similar to that for all adverse events.

Phase III All Patients Cohort

Despite the longer duration of treatment in this group, OM/AML was associated with a similar incidence of patients reporting adverse events (50.4 %) as its components administered as monotherapies (OM 43.4 % and AML 43.4 %), and a lower incidence than placebo (56.8 %). For the open-label cohort, addition of HCTZ to the combination was associated with an increase in the incidence of adverse events (61.1 %). In each group, the majority of adverse events were mild or moderate in severity and the distribution by maximum severity was similar across the groups, as was the pattern for drug-related adverse events.

Subgroup Analysis of Adverse Events

There was no difference in the incidence of adverse events in the OM/AML combination group for patients aged < 65 years (51.3%), ≥ 65 years (47.5%), and ≥ 75 years (52.6%). There was no difference in the incidence of adverse events in the OM/AML combination group for male (47.6%) and female patients (54.1%).

However, the incidence of oedema peripheral appeared higher in females (15.0%) than males (8.4%), and this pattern was observed for all the treatment groups, including placebo and is a recognised phenomenon. There were no clinically relevant differences observed between Caucasian and non-Caucasian races.

Most Common Adverse Events and Drug-related Adverse Events

Phase III Double-blind Cohort

The most commonly reported adverse events in the OM/AML group were general disorders and administration site conditions, or nervous system adverse events. The adverse events reported by ≥ 1% of patients in any group are summarised in Table 14. Oedema peripheral was reported at a higher incidence on active treatment versus placebo; however with a slightly lower incidence on OM/AML than on AML monotherapy (7.4 % on placebo, 8.0 % on OM, 10.5 % on AML, and 8.3% on OM/AML). The incidence of oedema was lower for OM/AML than for AML monotherapy (1.9 % on placebo, 1.7 % on OM, 4.5 % on AML, and 2.9 % on OM/AML).

Headache, dizziness, fatigue, back pain, pitting oedema and nausea were all less common on the active treatments than on placebo. Cough was reported at similar incidence in all the active treatment groups, which was higher than in the placebo group. The incidences of headache and hypertension were notably lower for the active treatment groups than for the placebo group.

As would be expected, oedema peripheral, oedema and pitting oedema were more common for combinations containing 10 mg AML versus the 5 mg dose. However, it was noted that at both AML dose levels, the incidence of these events was highest for the combinations containing OM 10 mg suggesting that the combinations containing OM at 20 mg and 40 mg were more effective at reducing the oedema events associated with AML therapy. No other potentially dose related patterns were identified for the common adverse events.

The profile of drug-related adverse events was similar across the treatments: most commonly general disorders and administration site conditions, or nervous system adverse events. The drug-related adverse events reported by ≥ 1% of patients in any group are summarised in Table 15. The incidence of oedema was lower for the OM/AML then for AML. Headache, dizziness and fatigue were all less common on the active treatments than on placebo. There was no evidence of a dose-relationship for drug-related adverse events.

Phase III Open-label Cohort

Addition of HCTZ to the combination was associated with an increase in the incidence of adverse events. The incidence of oedema peripheral and oedema were highest for the OM/AML 40/10 mg + HCTZ 25 mg group but similar for the OM/AML 40/10 mg and OM/AML 40/10 mg + HCTZ 12.5 mg groups. Otherwise, the profile of adverse events on OM/AML + HCTZ was as would be expected from the known safety profile of HCTZ.

Table 14: Adverse events with ≥ 1% incidence in the any combined treatment group – Phase III double-blind cohort

N (%) patients with:	Placebo (N=162)	OM (N=663)	AML (N=512)	OM/AML (N=2003)
General disorders and administration site conditions	30 (18.5)	87 (13.1)	97 (18.9)	280 (14.0)
Oedema peripheral	12 (7.4)	53 (8.0)	54 (10.5)	167 (8.3)
Oedema	3 (1.9)	11 (1.7)	23 (4.5)	58 (2.9)
Fatigue	6 (3.7)	13 (2.0)	8 (1.6)	37 (1.8)
Pitting oedema	5 (3.1)	9 (1.4)	9 (1.8)	27 (1.3)
Chest pain	2 (1.2)	3 (0.5)	5 (1.0)	5 (0.2)
Chest discomfort	2 (1.2)	3 (0.5)	0	3 (0.1)
Nervous system disorders	29 (17.9)	78 (11.8)	38 (7.4)	170 (8.5)
Headache	23 (14.2)	42 (6.3)	25 (4.9	82 (4.1)
Dizziness	9 (5.6)	26 (3.9)	9 (1.8)	55 (2.7)
Infections and infestations	13 (8.0)	48 (7.2)	49 (9.6)	140 (7.0)
Nasopharyngitis	2 (1.2)	2 (0.3)	4 (0.8)	28 (1.4)
Urinary tract infection	1 (0.6)	4 (0.6)	6 (1.2)	21 (1.0)
Upper respiratory tract infection	3 (1.9)	5 (0.8)	9 (1.8)	14 (0.7)
Sinusitis	2 (1.2)	7 (1.1)	2 (0.4)	6 (0.3)
Musculoskeletal and connective tissue disorders	15 (9.3)	44 (6.6)	38 (7.4)	123 (6.1)
Back pain	5 (3.1)	11 (1.7)	8 (1.6)	30 (1.5)
Arthralgia	3 (1.9)	7 (1.1)	8 (1.6)	16 (0.8)
Muscle spasms	2 (1.2)	5 (0.8)	3 (0.6)	14 (0.7)
Gastrointestinal disorders	11 (6.8)	33 (5.0)	34 (6.6)	110 (5.5)
Nausea	5 (3.1)	8 (1.2)	5 (1.0)	20 (1.0)
Diarrhoea	2 (1.2)	5 (0.8)	7 (1.4)	18 (0.9)
Dyspepsia	2 (1.2)	3 (0.5)	2 (0.4)	10 (0.5)
Toothache	0	3 (0.5)	7 (1.4)	7 (0.3)
Abdominal pain	3 (1.9)	2 (0.3)	1 (0.2)	7 (0.3)
Investigations	9 (5.6)	25 (3.8)	15 (2.9)	74 (3.7)
Electrocardiogram abnormal	2 (1.2)	0	1 (0.2)	0
Respiratory, thoracic, and mediastinal disorders	6 (3.7)	25 (3.8)	14 (2.7)	68 (3.4)
Cough	1 (0.6)	7 (1.1)	6 (1.2)	27 (1.3)
Dyspnoea	3 (1.9)	5 (0.8)	3 (0.6)	7 (0.3)
Epistaxis	2 (1.2)	2 (0.3)	0	4 (0.2)
Skin and subcutaneous tissue disorders	10 (6.2)	18 (2.7)	13 (2.5)	49 (2.4)
Rash	2 (1.2)	1 (0.2)	7 (1.4)	11 (0.5)
Hyperhidrosis	2 (1.2)	1 (0.2)	0	2 (0.1)
Vascular disorders	12 (7.4)	22 (3.3)	8 (1.6)	31 (1.5)
Hypertension	10 (6.2)	11 (1.7)	2 (0.4)	3 (0.1)
Injury, poisoning, and procedural complications	5 (3.1)	16 (2.4)	4 (0.8)	40 (2.0)
Joint sprain	2 (1.2)	0	1 (0.2)	5 (0.2)
Psychiatric disorders	2 (1.2)	13 (2.0)	8 (1.6)	23 (1.1)
Insomnia	2 (1.2)	3 (0.5)	3 (0.6)	10 (0.5)
Renal and urinary disorders	3 (1.9)	1 (0.2)	9 (1.8)	16 (0.8)
Haematuria	3 (1.9)	0	0	2 (0.1)
Eye disorders	3 (1.9)	4 (0.6)	2 (0.4)	18 (0.9)
Vision blurred	2 (1.2)	1 (0.2)	0	4 (0.2)

Adverse events are ordered by incidence on OM/AML within a SOC

SOC: System Organ Class

Table 15: Drug-related adverse events with ≥ 1% incidence in the OM/AML combined treatment group – Phase III double-blind cohort

N (%) patients with:	Placebo (N=162)	OM (N=663)	AML (N=512)	OM/AML (N=2003)
General disorders and administration site conditions	18 (11.1)	60 (9.0)	68 (13.3)	202 (10.1)
Oedema peripheral	9 (5.6)	35 (5.3)	45 (8.8)	125 (6.2)
Oedema	2 (1.2)	9 (1.4)	15 (2.9)	41 (2.0)
Fatigue	5 (3.1)	13 (2.0)	5 (1.0)	25 (1.2)
Pitting oedema	2 (1.2)	6 (0.9)	4 (0.8)	17 (0.8)
Nervous system disorders	15 (9.3)	46 (6.9)	15 (2.9)	82 (4.1)
Headache	11 (6.8)	26 (3.9)	8 (1.6)	43 (2.1)
Dizziness	6 (3.7)	19 (2.9)	6 (1.2)	35 (1.7)
Gastrointestinal disorders	7 (4.3)	10 (1.5)	9 (1.8)	34 (1.7)
Nausea	3 (1.9)	2 (0.3)	2 (0.4)	7 (0.3)
Vascular disorders	9 (5.6)	11 (1.7)	1 (0.2)	16 (0.8)
Hypertension	7 (4.3)	5 (0.8)	0	1 (0.0)

Adverse events are ordered by incidence on OM/AML within a SOC

Phase III All Patients Cohort

In the Phase III all patients cohort, the most common adverse events occurred in the system organ classes of general disorders and administration site conditions, infections and infestations, and nervous system disorders. The most common adverse events on OM/AML were oedema peripheral, headache, dizziness and oedema. The incidence of oedema peripheral was highest on OM/AML + HCTZ (the incidences were 7.4 % on placebo, 8.0 % on OM, 10.5 % on AML, 11.3 % on OM/AML, and 15.1 % on OM/AML + HCTZ). However, for oedema, the addition of HCTZ to the combination did not appear to increase the incidence (3.8 % for OM/AML and for OM/AML + HCTZ).

The incidence of headache was lower on each of the active treatments than on placebo, and the incidence of dizziness in each active group was similar to or lower than the incidence on placebo. There were no apparent differences in incidence of other adverse events among the groups.

The most common (≥ 1% in any group) drug-related adverse events by system organ class and preferred term are summarised in Table 16. 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. The following drug-related adverse events were reported by ≥ 1 % of patients in the OM/AML group: oedema peripheral, dizziness, headache, oedema, fatigue and pitting oedema.

Table 16: Drug-related adverse events with ≥ 1% incidence in any combined treatment group – Phase III all patients cohort

N (%) patients with:	Placebo (N=162)	OM (N=663)	AML (N=512)	OM/AML (N=2892)	OM/AML +HCTZ (N=755)
General Disorders and Administration Site Conditions	18 (11.1)	60 (9.0)	68 (13.3)	391 (13.5)	114 (15.1)
Oedema peripheral	9 (5.6)	35 (5.3)	45 (8.8)	252 (8.7)	85 (11.3)
Oedema	2 (1.2)	9 (1.4)	15 (2.9)	82 (2.8)	18 (2.4)
Fatigue	5 (3.1)	13 (2.0)	5 (1.0)	46 (1.6)	7 (0.9)
Pitting oedema	2 (1.2)	6 (0.9)	4 (0.8)	37 (1.3)	8 (1.1)
Nervous System Disorders	15 (9.3)	46 (6.9)	15 (2.9)	160 (5.5)	31 (4.1)
Dizziness	6 (3.7)	19 (2.9)	6 (1.2)	80 (2.8)	22 (2.9)
Headache	11 (6.8)	26 (3.9)	8 (1.6)	68 (2.4)	9 (1.2)
Vascular Disorders	9 (5.6)	11 (1.7)	1 (0.2)	40 (1.4)	15 (2.0)
Hypotension	0 (0.0)	1 (0.2)	0 (0.0)	25 (0.9)	10 (1.3)
Hypertension	7 (4.3)	5 (0.8)	0 (0.0)	2 (0.1)	0 (0.0)
Gastrointestinal Disorders	7 (4.3)	10 (1.5)	9 (1.8)	56 (1.9)	11 (1.5)
Nausea	3 (1.9)	2 (0.3)	2 (0.4)	12 (0.4)	4 (0.5)
Investigations	4 (2.5)	10 (1.5)	3 (0.6)	48 (1.7)	19 (2.5)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	9 (1.2)
Renal and Urinary Disorders	1 (0.6)	0 (0.0)	6 (1.2)	10 (0.3)	14 (1.9)
Pollakiuria	0 (0.0)	0 (0.0)	3 (0.6)	4 (0.1)	10 (1.3)

Adverse events are ordered by incidence on OM/AML within a SOC

Deaths, Serious Adverse Events and Withdrawals Due to Adverse Events

There were three deaths during the course of the clinical development program: one patient receiving placebo was murdered and in the OM/AML combination group one patient died due to cerebral haemorrhage and another was shot in the head. None of these deaths were considered to be treatment-related.

The incidence of serious adverse events (SAEs) was low across all treatment groups. The majority of SAEs in the Phase III double-blind cohort were reported for only one patient. Only one SAE (cerebrovascular accident) was considered related to treatment as the investigator considered BP to be too high.

For the Phase III open-label cohort only one SAE (non-cardiac chest pain) was considered related to treatment. A review of the incidence and specific types of SAEs, as well as an assessment of potential relationship between the SAEs and study medication, suggested that there were no trends for the occurrence of any specific SAEs in patients on either OM or AML monotherapy or patients on OM/AML.

In the Phase III double-blind cohort, SAEs were reported for three patients (1.9%) on placebo, seven (1.1%) on OM monotherapy, three (0.6%) on AML monotherapy and 21 (1.0%) on OM/AML combination therapy. The majority of SAEs were reported for only one patient. However, two patients on OM/AML had SAEs of atrial fibrillation, two patients on OM monotherapy had cerebrovascular accidents and one patient on AML monotherapy and one on OM/AML had ischaemic stroke.

Only one SAE was considered related to treatment. The patient, a 58-year old Black female receiving OM 20 mg in study 301, experienced a cerebrovascular accident that the Investigator considered probably related to study medication due to BP being too high. The patient was discontinued from the study and the event resolved after 5 days.

A review of the incidence and specific types of SAEs, as well as an assessment of potential relationship between the events and study medication, suggest that there were no trends for the occurrence of any specific SAEs in patients on either OM or AML monotherapy or patients on OM/AML combination therapy.

In the Phase III open-label cohort, 37 patients (1.6%) on OM/AML 40/5 mg, 24 (1.9%) on OM/AML 40/10 mg, 15 (2.0%) on OM/AML 40/10 mg + HCTZ 12.5 mg and 18 (4.1%) on OM/AML 40/10 mg + HCTZ 25 mg experienced SAEs. A further four patients (4.7%) on other treatment regimens also had SAEs reported in the Phase III open-label cohort. As observed for the double-blind cohort, the majority of SAEs in the Phase III open-label cohort were reported by one or two patients. The most common SAEs, reported at an incidence of 0.2% with all groups combined were: osteoarthritis (five patients) and coronary artery disease (four patients). Only one patient, a 64 year old White female who experienced mild non-cardiac chest pain of 2 days duration that was considered by the Investigator to have had an SAE possibly related to the study medication (patient received OM/AML 40/5 mg in study 301). No other SAEs were considered related to study medication.

The combination of OM/AML was associated with a lower incidence of withdrawals due to adverse events than placebo and OM and AML administered as monotherapies. In the Phase III double-blind cohort, the most common adverse event that led to discontinuation was hypertension, which was most common for placebo (6.2 %) and ranged from 1.2 % to 1.5 % on OM 10 to 40 mg monotherapy, was 0.6 % on AML 5 mg and not reported for AML 10 mg, and was observed at the following doses of OM/AML combination: 0.1 % for 20/5 mg and 0.2 % for 40/5 mg. The next most common adverse event that led to withdrawal was oedema peripheral, reported for 0.6 % on OM 40 mg, 1.8 % on AML 10 mg, 2.5 % on OM/AML 10/10 mg, 0.1 % on OM/AML 20/5 mg, 0.9 % on OM/AML 20/10 mg, and 1.8 % on OM/AML 40/10 mg. The incidence of withdrawal due to oedema peripheral appeared to be more common in regimens using AML 10 mg. The incidence of withdrawal due to oedema peripheral was lower for the OM/AML than for monotherapy with AML 10 mg.

Adverse Events of Special Interest

Combined Oedema Events

A separate post-hoc analysis was conducted in order to assess the incidence of combined oedema events in study 301 versus the two other double-blind studies.

During the double-blind period of study 301, the incidence of combined oedema events was markedly greater in the AML 10 mg group (36.2 %) compared with the OM monotherapy group (9.9 % to 18.5 %) and the groups that used AML 10 mg as one of their treatment components (22.8 % to 27.2 %). There appeared to be a progressive decrease in the incidence of oedema when AML 10 mg was combined with OM 10 mg, 20 mg, and 40 mg (27.2 %, 25.6 %, and 22.8 %, respectively).

In studies 302 and 303, the incidence of combined oedema events among patients was similar across the treatment regimens, 2.1 % for AML 5 mg monotherapy, 1.1 % for OM 20 mg monotherapy, 3.7 % for OM/AML 10/5 mg, 1.4 % for 20/5 mg, 1.6 % for 40/5 mg, 2.8 % for 20/10 mg and 1.8 % for 40/10 mg. According to the AML Australian Product Information (PI), the incidence of oedema reported in clinical trials with AML is 0.6 %, 3.0 %, and 10.8 % for placebo, the 5 mg dose, and the 10 mg dose, respectively (Norvasc PI, March 2007). The incidence rate of peripheral oedema for OM, as reported in the Australian PI, is between 0.5 % and 1.0 % for the various doses of OM (Olmetec PI, June 2008). The higher incidence in study 301 is considered to be due to the design of study 301; the specific questioning and assessment regarding oedema are considered to have led to an increased reporting of oedema as an adverse event in comparison with the other studies.

Other Adverse Events of Special Interest

Other adverse events of special interest that were analysed included lack of drug effect, hypotension, headache, dizziness and vertigo, syncope, renal-related events and hepatic-related events.

Renal events were reported at a higher incidence in the OM/AML 40/10 mg + HCTZ 25 mg group in comparison with the other groups; however the incidence of these events was low and not of clinical concern. Lack of drug effect also appeared to be more frequent in the OM/AML 40/10 mg + HCTZ 25 mg group than the other groups but this probably reflects selection bias (patients who had not responded adequately at the lower dose groups entered this group).

No safety signals were identified on review of the other adverse events of special interest for the Phase III double-blind cohort, or for the Phase III open-label cohort.

Laboratory Findings and ECGs

For the Phase III double-blind cohort, changes in chemistry and haematology parameters in all groups were small and not considered to be of clinical relevance. The occurrence of newly occurring marked laboratory abnormalities during treatment was low in each group and there was no pattern to suggest a dose-relationship for any of the parameters examined. There was no pattern to suggest any trends of clinical concern by examination of the shifts to worst severity for any laboratory parameters.

For the Phase III open-label cohort, the triple combination (OM/AML+ HCTZ) appeared to be associated with larger decreases in sodium and potassium, and larger increases in ALT, AST, blood urea nitrogen (BUN), creatinine, glucose and total protein than the dual (OM/AML) combination. Many of these trends are known to be associated with HCTZ treatment. Furthermore, platelet and WBC counts appeared increased in the triple combination compared with the dual combination, which may reflect reduced plasma volume following HCTZ-induced diuresis. Overall, the changes in chemistry and haematology parameters in the Phase III open-label cohort in all groups were small and not considered to be of clinical relevance. The incidences of newly occurring marked laboratory abnormalities were low in each group.

There were no clinically relevant changes in electrocardiogram (ECG) parameters observed in the Phase III double-blind or Phase III open-label cohorts.

Overdose, Withdrawal and Rebound

No clinical experience of overdosage is available. No clinical or nonclinical studies relevant to abuse potential have been performed. No abuse potential is known for angiotensin- receptor blockers or calcium channel blockers. No withdrawal or rebound effects are known with OM or AML.

Comment

Overall the safety analyses support the use of OM/AML combination, with a safety profile that was shown to be similar to the monotherapies, with the exception of oedema events, where the incidence was lower with the combination therapy. No unexpected safety concerns emerged in the clinical trial program.

Clinical Summary and Conclusions

In this application the sponsor sought approval for Sevikar for the treatment of hypertension for use:

- as initial therapy in patients likely to need multiple antihypertensive agents to achieve their target BP goal, and

- in patients whose blood pressure is not adequately controlled on either: angiotensin receptor blocker, angiotensin converting enzyme (ACE) inhibitor or dihydropyridine calcium channel antagonist monotherapies.

The data presented for evaluation consisted of 13 pharmacokinetic (PK) studies, and 3 pivotal efficacy and safety studies. The 3 pivotal clinical efficacy and safety studies included 3233 randomised patients in total, of whom 2892 received treatment with OM/AML combination therapy (746 for at least 9 months overall and 173 for at least 12 months overall). The studies included 691 elderly patients aged ≥ 65 years with 613 elderly patients being exposed to OM/AML combination therapy.

The double-blind period of the factorial ***study 301*** demonstrated that OM/AML combination therapy was statistically superior to its individual components at corresponding doses in patients with mild to severe hypertension. The effects of OM/AML treatment generally increased with increasing dose of each component.

In ***study 302***, in patients whose BP was not adequately controlled by OM 20 mg monotherapy, addition of AML 5 or 10 mg provided statistically significant and clinically relevant benefit compared with addition of placebo.

In ***study 303 (Period II)***, in patients whose BP was not adequately controlled by AML 5 mg monotherapy, addition of OM 10, 20 or 40 mg provided statistically significant and clinically relevant benefit compared with the addition of placebo.

The results for trough-to-peak ratios in study 301 and for the ABPM data in studies 302 and 303 confirmed that the efficacy of OM/AML treatment was evident throughout the 24-hour dose interval. In addition the efficacy of OM/AML combination therapy persisted during long-term treatment, with no evidence of the development of tolerance to treatment.

Sub-group analyses of efficacy did not indicate any need for dose adjustment based on age, gender, hypertension severity, diabetic status, race or BMI.

The safety analyses support the use of OM/AML combination, with a safety profile that was shown to be similar to the monotherapies, with the exception of oedema events, where the incidence was lower with the combination therapy. No unexpected safety concerns emerged in the clinical trial program.

EU guidelines suggest that it is necessary to show that any additional safety concerns (incidence/seriousness /severity/outcome of adverse events/adverse drug reactions) do not outweigh the additional benefit of the combination.

It was the opinion of the clinical evaluator that the data presented in this application support approval of combination OM/AML treatment for use as first-line and second line treatment of hypertension.

There is no product with 10 mg OM or 2.5 mg AML. This is not likely to problematic in the clinical setting. In the EU the lowest approved daily dose of OM is 10 mg; however it is recommended that non-responders to AML 5 mg should be switched directly to the OM/AML 20/5 mg combination.

In study 303, in patients whose BP was not adequately controlled by AML 5 mg the BP lowering effect of adding OM 20 mg was numerically superior to that of adding OM 10 mg.

The efficacy data overall suggest that the OM 10 mg and AML 2.5 mg are not likely to be clinically useful.

Recommendation

The evaluator recommended that this application for Sevikar should be approved**.** The indication as proposed by the sponsor (below) is adequately supported by the data presented for evaluation.

Sevikar is indicated for:

- initial therapy in patients likely to need multiple antihypertensive agents to achieve their target BP goal, and
- treatment of hypertension in patients whose blood pressure is not adequately controlled on either angiotensin receptor blocker, angiotensin converting enzyme (ACE) inhibitor or dihydropyridine calcium channel antagonist monotherapies.

V. Pharmacovigilance Findings

A Risk Management Plan was submitted for evaluation. This was comprehensive and included summaries of the clinical data, a pharmacovigilance plan and an outline of risk minimisation activities that will be conducted. The Risk Management Plan was considered adequate.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval of the application was recommended with respect to chemistry, quality control and bioavailability.

Details of this submission were presented at the 130th meeting of PSC in Jan 2010. The PSC endorsed all questions raised by the quality evaluator. It considered the justification for using an overseas formulation of amlodipine tablets in the bioavailability studies acceptable but thought that the CMI should include a statement in relation to the interaction with grapefruit juice. The Delegate endorsed this request.

Six potential formulations (A, B, C, D, G and H) of the olmesartan/amlodipine fixed-dose combination were evaluated in PK studies. Formulation G was selected as the primary formulation for commercial use.

The relevant bioavailability studies were also evaluated by the clinical evaluator and will be summarised in that section.

There was no data in the submission comparing the 20/5, 20/10 and 40/5 mg fixed-dose combinations to the separate monotherapies or to the 40/10 mg fixed-dose combination. However, a justification for this was submitted and found to be acceptable on both chemistry and clinical grounds.

The submission did not contain any data comparing an Australian registered amlodipine tablet to the Antacal amlodipine tablet used in the Phase III clinical studies. However, a justification for this was submitted and found to be acceptable on both chemistry and clinical grounds.

Nonclinical

There were no nonclinical objections to the registration of Sevikar for the treatment of hypertension.

No significant novel toxicities were noted for the olmesartan medoxomil/amlodipine besylate combination in a well-conducted, GLP-compliant, 13-week toxicology study in rats with the drug orally administered.

The toxicities observed have been described previously for these drugs, or for drugs of the same class, and reflect target organ toxicities that are able to be monitored in the clinic. As both active

compounds have been approved and on the market for some years, and as there is extensive non-clinical and clinical data available (for both compounds alone and in various combinations), there were no novel clinical safety concerns raised by the non-clinical data.

Clinical

Pharmacokinetics

The supportive and secondary studies evaluated the earlier potential formulations (A, B, C, D and H) which were not carried forward. The pivotal studies examined formulation G which was the formulation selected to be carried forward. While the clinical evaluator has evaluated all of these studies in detail, this overview will focus only on the pivotal studies.

Study CS-8663-A-U101 (drug-drug interaction study) – This study demonstrated that co-administration of separate olmesartan and amlodipine did not affect the steady-state maximum or total exposure of either compound at their highest indicated doses, olmesartan 40 mg and amlodipine 10 mg.

Study SE-866/31 (drug-drug interaction study) – This study showed no PK interaction between the lower doses of olmesartan 20 mg and amlodipine under fasting conditions.

Study CS8663-A-E-102 (bioequivalence of marketed amlodipine formulations) – In this study, three different marketed formulations of amlodipine as besylate from the UK, USA and Italy, were shown to be bioequivalent. In the pivotal efficacy studies, the Italian commercially available innovator product was the formulation of amlodipine used. The results of any BE/BA studies comparing amlodipine in the fixed-dose combinations with the Italian commercially available innovator amlodipine product can be extrapolated to the other two formulations.

Study CS8663-A-U109 (bioavailability study for formulation G) – This study demonstrated the bioequivalence of a fixed-dose combination of olmesartan/amlodipine 40/10 mg relative to co-administration of the separate entities as olmesartan medoxomil 40 mg and amlodipine (Italian commercially available innovator product) 10 mg.

Study CS8663-A-U110 (Definitive Food Effect Study using Formulation G) – This study demonstrated that the pharmacokinetics of olmesartan and amlodipine when administered as a fixed-dose combination at the highest strength (40/10 mg) were equivalent during the fasting state and following a high fat meal.

Study CS8663-A-U111 (Bioavailability Study evaluating fixed-dose combinations intended for commercial use, that is, Formulation G) – This study showed that the rate and extent of bioavailability of both olmesartan and amlodipine from the highest-strength fixed-dose combination tablet, 40/10 mg were bioequivalent to the corresponding separate tablet, that is, to olmesartan medoxomil 40 mg and 10 mg amlodipine (Italian commercially available innovator product), respectively, when those separate tablets were co-administered under fasting conditions.

Study CS8663-A-U112 (Dose Proportionality Study) – This study showed that the AUC for olmesartan following oral administration of 10, 20 or 40 mg increased in a dose-proportional manner when administered in a fixed-dose combination with either amlodipine 5 or 10 mg. A slightly less than dose-proportional increase in C_{max} for olmesartan in the same situation was observed but this was not of clinical significance. The reverse case held for both AUC and C_{max}, namely both the AUC and C_{max} of amlodipine following oral administration of 5 or 10 mg increased in a dose-proportional manner when administered in a fixed-dose combination with olmesartan 10, 20 or 40 mg.

Summary of Pharmacokinetics

For all formulations evaluated, the PK profiles of olmesartan and amlodipine were unaffected by tablet type and whether concomitantly administered or not. The bioavailabilities of both olmesartan and amlodipine were shown to be unaffected by food.

Efficacy

The three pivotal clinical efficacy and safety studies included 3233 randomised patients in total, of whom 2892 received treatment with olmesartan/amlodipine fixed-dose combination therapy (746 for at least 9 months and 173 for at least 12 months). Overall, the studies included 691 elderly patients aged at least 65 years (of whom 83 were aged at least 75 years) and of these 613 elderly patients (including 76 patients aged at least 75 years) were exposed to the fixed-dose combination therapy.

Study CS8663-A-U301

Study 301 comprised a 1-2 week wash out period (Period I), an 8-week factorial design, randomised, double-blind, parallel-group period (Period II) and a 44-week open-label extension period (Period III). Patients were eligible for randomisation into Period II if they had a seated diastolic blood pressure, SeDBP 95 – 120 mm Hg. The 8-week, double-blind period of the study (Period II) included 12 parallel treatment groups. Patients entering Period III initially received olmesartan/amlodipine 40/5 mg which was up-titrated to 40/10 mg, followed by the addition of HCTZ 12.5 mg, then 25 mg if needed (in those patients whose SeDBP $\geq$ 90 mm Hg or SeSBP $\geq$ 140 mm Hg at the previous dose).

The primary objective during Period II (day 1 to week 8) was to demonstrate that olmesartan + amlodipine co-administration was more efficacious for lowering of SeDBP than each of its corresponding monotherapy components. There were a number of secondary efficacy endpoints. The treatment groups were comparable with respect to demographics. The results for mean change in SeDBP and SeSDP during Period II are shown in Tables 5 and 6.

Mean reductions in seated DBP at week 8 were numerically larger in the combination therapy groups than in the monotherapy groups. In the combination therapy groups with amlodipine 5 and 10 mg, increasing doses of olmesartan 10, 20 and 40 mg resulted in numerically larger mean reductions in seated DBP. Likewise, the reverse case held. In the combination therapy groups with olmesartan 10, 20 and 40 mg, increasing doses of amlodipine 5 and 10 mg resulted in numerically larger mean reductions in seated DBP.

The mean reduction in seated DBP at week 8 was statistically significantly larger for each combination therapy than for the corresponding component monotherapies. The above results for seated DBP were also repeated at week 2. Similar mean reductions in seated SBP were also observed, again at both time points, weeks 2 and 8.

The percentages of patients who reached their blood pressure goal were higher in the olmesartan/amlodipine combination therapy groups than in the corresponding monotherapy groups. Approximately 50% of patients on one of the higher dose combination therapies (olmesartan/amlodipine 10/10, 20/10, 40/5 or 40/10) reached their blood pressure goal at week 8. However, it should be noted that, while there was a steady increase in this proportion in those groups held on amlodipine 5 mg while the dose of olmesartan was increased (from 35.0% to 51.0%), there was no such pattern in those groups held on amlodipine 10 mg while the dose of olmesartan was increased. In the latter three groups, the peak was achieved for the olmesartan/amlodipine 20/10 mg group (53.2%) while the proportion for the olmesartan/amlodipine 40/10 mg group slipped back to 49.1%, the same as that for the olmesartan/amlodipine 10/10 mg group (Table 7).

Next in the evaluation is a report on the probability of reaching particular blood pressure thresholds as a function of baseline blood pressure. These probabilities are the result of an additional efficacy analysis based on the US FDA guidance, "*Points to Consider in generating graphs for initial therapy with combination anti-hypertensive drugs*". The probability curves for each treatment have been generated *post hoc* and estimated by logistic regression modelling from all available data for that treatment group.

Study CS8663-A-E302

Study 302 was a randomised, double-blind, parallel-group trial consisting of a 1- to 2-week taper-off phase for patients being treated with anti-hypertensive medication other than olmesartan 20 or 40 mg and 2 treatment periods, Periods I & II. Period I was an 8-week open-label period during which all patients were on monotherapy with olmesartan 20 mg. At the end of Period I only non-responders were eligible to be randomised and enter Period II. Patients whose BP was controlled on olmesartan 20 mg at week 8 discontinued at that point. Period II was an 8-week double-blind period during which patients non-responsive to olmesartan 20 mg were assigned randomly in a 1:1:1 ratio to one of three treatment groups: olmesartan 20 mg + placebo or + amlodipine 5 mg or + amlodipine 10 mg. In effect, this was an add-on study which simply reflects standard clinical practice.

The primary objective was to demonstrate the additional anti-hypertensive efficacy in lowering trough sitting diastolic blood pressure by adding amlodipine 5 or 10 mg to the treatment regimen in patients with hypertension not adequately controlled on olmesartan 20 mg alone. There were a number of secondary objectives. Patients enrolled in this study included males and females at least 18 years of age with SBP ≥ 160 mm Hg and DBP ≥ 100 mm Hg.

The results for the primary efficacy endpoint are displayed in Table 8. Treatment with olmesartan and amlodipine combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with olmesartan 20 mg + placebo therapy. These reductions were -2.7 mm Hg for olmesartan 20 mg + amlodipine 5 mg ($p = 0.0006$) and -3.2 mm Hg for olmesartan 20 mg + amlodipine 10 mg ($p < 0.0001$). There appears to have been no comparison between the two latter treatment groups, that is, between olmesartan/amlodipine 20/5 mg and olmesartan 20/10 mg although it would not be expected that there would have been a statistically significant difference between reductions of -2.7 mm Hg and -3.2 mm Hg.

There were similar statistically significant reductions in mean sitting systolic blood pressure.

The proportions of patients reaching BP goal (<140/90 mm Hg for non-diabetic patients or < 130/80 mm Hg for diabetic patients) were significantly greater in the add-on amlodipine groups than in the add-on placebo group (Table 9). However, there was no significant difference between the two add-on amlodipine groups in these proportions (64.3% for the amlodipine 20/5 mg group and 68.4% for the amlodipine 20/10 mg group).

Study CS8663-A-U303

Study 303 was a 52-week, Phase III, randomised, parallel-group trial with 4 periods: Period I, an 8-week, open-label treatment period with amlodipine 5 mg monotherapy; Period II, an 8-week double-blind treatment period with randomisation to a fixed combination of olmesartan and amlodipine; Period III, an 8-week, double-blind treatment period with dose up-titration if needed and Period IV, a 28-week, open-label, extension period with possible dose titration.

After 1-2 weeks of tapering off previous anti-hypertensive medication, patients eligible for the study entered an 8-week open-label, run-in period on amlodipine 5 mg (Period I). Patients who were already on amlodipine 5 or 10 mg at screening entered directly into Period I on amlodipine 5 mg without any tapering off. To enter Period I, newly diagnosed hypertensive patients and patients previously on medications other than amlodipine 5 or 10 mg must have had a mean sitting DBP ≥

100 mm Hg and a mean sitting SBP ≥ 160 mm Hg. Patients on amlodipine 5 or 10 mg must have had, in order to enter Period I, a mean sitting DBP ≥ 90 mm Hg and a mean sitting SBP ≥ 140 mm Hg.

At the end of Period I, patients who did not respond adequately to amlodipine 5 mg monotherapy (non-responders defined as those with BP, either element ≥ 140/90) were assigned randomly to double-blind treatment for 8 weeks with olmesartan 10, 20 or 40 mg or placebo in addition to amlodipine 5 mg, that is, to one of four treatment options: olmesartan/amlodipine 0/5, 10/5, 20/5 or 40/5 mg. Patients who responded adequately to amlodipine 5 mg monotherapy discontinued from the study at this point.

At the end of Period II, patients whose BP was not adequately controlled (non-responders defined essentially as above) underwent dose titration during Period III. Patients randomised to combination therapy with olmesartan/amlodipine 0/5,10/5, 20/5 & 40/5 mg had their doses titrated to 20/5, 20/5, 40/5 & 40/10 mg, respectively. Patients whose BP was adequately controlled at the end of Period II remained on the same randomised treatment during Period III. There was no allowance for titration from 0/5 to 10/5 with the inevitable consequence that some patients would have been treated with an unnecessarily high dose.

At the end of Period III, patients entered a 28-week, open-label, extension period (Period IV). All patients initially received open-label olmesartan/amlodipine 40/5 mg. If the patient's BP was inadequately controlled at this dose (non-responders as above), investigators could titrate first to olmesartan/amlodipine 40/10 mg and then to triple therapy with olmesartan/amlodipine/hydrochlorothiazide 40/10/12.5 mg and if needed to 40/10/25 mg.

The primary objective was to demonstrate the additional anti-hypertensive efficacy in lowering sitting diastolic blood pressure by adding olmesartan 10, 20 or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on amlodipine 5 mg alone.

There were a number of secondary objectives. All active treatments of add-on olmesartan provided a statistically significant additional BP-lowering effect compared with add-on placebo (Table 10). While the study was powered to detect a significant difference between each of the active olmesartan add-on groups and the placebo add-on group, it was not powered to detect such differences between the active olmesartan add-on groups themselves. There was no add-on benefit between the two groups olmesartan/amlodipine 20/5 and 40/5 mg, with mean DBP reductions of -3.7 mm Hg and -3.8 mm Hg, respectively. This has direct implications of the validity of any claim to first-line therapy and whether or not the study was powered sufficiently is immaterial. For if the study was powered appropriately, then the result is clearly not statistically significant and if the study was not powered appropriately, then that in itself raises doubts about the validity of any claim of being able to institute these combined therapies first-line. In other words, whatever the situation, there can be no clear guidance to practitioners about any difference in dose-response between olmesartan/amlodipine 20/5 and 40/5 mg, when titrating up from amlodipine 5mg. Also it should be noted that neither of these medications has actually been used first-line in this study. Both have only been employed after failure to respond to amlodipine 5 mg.

The proportions of patients reaching BP goal (<140/90 mm Hg for non-diabetic patients and < 130/80 mm Hg for diabetic patients) were significantly greater in the add-on olmesartan groups than in the add-on placebo group (Table 11). There was no difference in these proportions for the groups olmesartan/amlodipine 20/5 & 40/5 mg. The proportion (50.5%) on the higher of the two dosage strengths was less than that (53.5%) for the lower of the two dosage strengths.

For patients who remained on their randomised treatment regimen during Period III, the proportion who reached BP goal at week 24 was higher with olmesartan/amlodipine treatment than with placebo + amlodipine 5 mg. For patients whose dose regimen was titrated, successively higher proportions reached BP goal with each increase in dose combination of olmesartan + amlodipine.

This is true if one begins with the titration olmesartan/amlodipine 10/5 mg to 20/5 mg. Almost 60% (58.8%) of patients in the placebo + amlodipine 5 mg group achieved their BP goal by staying on that dosage regimen.

Justification for second-line therapy for switching patients on any angiotensin II receptor blocker (ARB), angiotensin converting enzyme (ACE) inhibitors or Dihydropyridine calcium channel blocker (CCB) monotherapy to Sevikar

The information provided in the submission and summarised in the evaluation report focussed on published literature comparing efficacy and safety of the various classes of anti-hypertensive agents.

Firstly, olmesartan is compared against each of the other ARBs, losartan, valsartan, irbesartan, candesartan and telmisartan. Only one dose of olmesartan was used in the studies, namely 20 mg. In the opinion of the Delegate, the comparisons with valsartan 80 mg and with candesartan 8 mg are potentially flawed because with these two latter drugs, there are two dose-titration steps available above the chosen dose. There is only one such step available above olmesartan 40 mg. All studies were short-term, 8 weeks. There was no head-to-head comparison with eprosartan.

The Delegate considered that the data comparing olmesartan with ACE inhibitors was even more deficient. Olmesartan has only been compared to two ACE inhibitors, namely enalapril and captopril, again in short-term studies. There are absolutely no data comparing it with any of the newer ACE inhibitors.

There are no specific data cited comparing amlodipine to any of the other dihydropyridine calcium channel blockers, felodipine, lercanidipine or nifedipine.

The sponsor responded to these comments of the Delegate highlighting that the basis for the majority of the evidence for transitioning patients was based on literature evidence. Although the TGA did require clarification and suggested a search strategy, this produced fewer results/publications and produced no inconsistent information. With regards to the Delegate's concerned about the doses and the length of the studies of the ARBs, although some of the doses reported in the literature may not be the "equipotent" doses, they were usually the approved starting doses. The investigation time frame (8 weeks) for antihypertensive agents was consistent with EU regulatory guidelines for hypertension (2-3 months) and Australian, EU and US clinical guidelines for altering or titrating dosages.

The sponsor reiterated that the clinical evaluator recommended approval, commenting that: "*Olmesartan has been shown to have an equal or greater efficacy compared to that of the currently available ARBs. In addition to equal or greater efficacy, there were no discernable differences between olmesartan and the other ARBs with regards to safety. This evidence suggests that as olmesartan is equivalent to other ARBs in terms of safety and efficacy then patients on other ARBs could be switched to Sevikar"*.

In addition, the clinical evaluator also noted that *"Dihydropyridine CCBs have been shown to have similar efficacy and safety profiles and therefore switching inadequately controlled patients from DHP CCBs to Sevikar would also seem reasonable"*

Finally, the Delegate noted that there is no evidence at all in this part of the submission which compares any of the possible dual combinations with the combination of olmesartan and amlodipine. For example, where is the efficacy and safety data comparing a combination of candesartan + lercanidipine or perindopril + felodipine SR with olmesartan + amlodipine?

The sponsor clarified and confirmed that the proposed indication does not include patients currently on combination therapy to be switched to Sevikar. Only patients whose BP is not well controlled on monotherapy within classes of ARBs or CCBs are proposed to be transitioned to Sevikar.

Summary of efficacy

The double-blind period of the factorial ***study 301*** demonstrated that olmesartan/amlodipine combination therapy was statistically and clinically superior to the individual components at corresponding doses in patients with mild to severe hypertension. This is demonstrated in Figure 1. There is a seamless increase in the reductions in seated DBP as one steps up either the olmesartan or the amlodipine doses.

In ***study 302,*** conducted in patients whose BP was not adequately controlled by olmesartan 20 mg monotherapy, addition of amlodipine 5 or 10 mg provided statistically significant and clinically relevant benefit compared with the addition of placebo.

In ***study 303 (Period II)***, in patients whose BP was not adequately controlled by amlodipine 5 mg monotherapy, addition of olmesartan 10, 20 or 40 mg provided statistically significant and clinically relevant benefit compared with the addition of placebo.

Safety

Extent of exposure

In the Phase III double-blind cohort, a total of 2003 patients received olmesartan/amlodipine treatment and the mean extent of exposure was 70.0 days (median 57 days). In the Phase III open-label cohort, a total of 2376 patients received olmesartan/amlodipine and the mean extent of exposure was 143.6 days (median 116.6 days).

Overall adverse events

In the Phase III double-blind cohort, olmesartan/amlodipine was associated with a lower incidence of patients reporting AEs (38.4%) than either of the components administered as monotherapies (olmesartan 43.4% and amlodipine 43.4% and placebo 56.8%). In the Phase III open-label cohort, the incidence of AEs increased with increasing the dose of amlodipine from 5 to 10 mg and with the addition of hydrochlorothiazide to the combination. In both groups the majority of AEs were mild or moderate in severity and the distribution by maximum severity was similar across the groups. There was no difference in the incidence of AEs in the combination groups by age (< 65 years, ≥ 65 years or ≥ 75 years).

Most common AEs and drug-related AEs

In the Phase III double-blind cohort the most commonly reported AEs in the olmesartan/amlodipine group were general and administration site conditions or nervous system AEs. Oedema peripheral was reported at a higher incidence on active treatment vs. placebo, however with a slightly lower incidence on olmesartan/amlodipine than on amlodipine monotherapy. Headache, dizziness, fatigue, back pain, pitting oedema and nausea were all less common on the active treatments than on placebo. Cough was reported at a similar incidence in all the active treatment groups but higher than in the placebo group. The profile of drug-related treatments was similar across the treatments. In the Phase III open-label cohort, addition of hydrochlorothiazide to the combination was associated with an increase in the incidence of AEs. In the Phase III all patients cohort, the following drug-related AEs were reported by $\geq 1\%$ of patients in the olmesartan/amlodipine group: oedema peripheral, dizziness, headache, oedema, fatigue and pitting oedema.

Deaths, Serious AEs and Withdrawals due to AEs

There were three (3) deaths, 1 in the placebo group and 2 in the combination groups, none considered treatment-related. The incidence of serious AEs was low across all treatment groups. Only one serious AE (CVA) was considered related to treatment as the investigator considered the BP to be too high. The combination of olmesartan/amlodipine was associated with a lower incidence of withdrawals due to AEs than placebo or olmesartan or amlodipine administered as monotherapies.

AEs of special interest

There appeared to be a progressive decrease in the incidence of oedema when amlodipine 10 mg was combined with olmesartan 10, 20 or 40 mg (27.2%, 25.6% and 22.8%, respectively). Renal events were reported at a higher incidence in the olmesartan/amlodipine 40/10 mg + hydrochlorothiazide 25 mg group in comparison with other groups. However, the incidence was low and not of clinical concern.

Laboratory Findings and ECGs

For the Phase III double-blind cohort, changes in chemistry and haematology parameters in all groups were small and not considered of clinical relevance. For the Phase III open-label cohort, the triple combination of olmesartan/amlodipine + hydrochlorothiazide was associated with larger decreases in sodium and potassium and larger increases in ALT, AST, creatinine, glucose and total protein compared with the dual combination. Many of these trends are known to be associated with hydrochlorothiazide treatment. There were no clinically relevant changes in ECG parameters observed in the Phase III double-blind or open-label cohorts.

Summary of Safety

Overall, the safety analyses support the use of the olmesartan/amlodipine combination, with a safety profile that was shown to be similar to the monotherapies, with the exception of oedema events, where the incidence was lower with the combination therapy. No unexpected safety concerns emerged in the clinical trial program.

Risk-Benefit Analysis

The clinical evaluator has recommended approval of the application for the indications sought by the sponsor.

Efficacy

The most relevant EU guideline is CPMP/EWP-238/95 Rev. 2, *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension*. For the claim of second-line therapy, it is usually necessary to establish the following:

- a statistically significant and clinically relevant additional blood pressure reduction on the fixed-dose combination in those patients who did not respond adequately to standard therapeutic doses of either monotherapy
- demonstration of statistically significant superior efficacy of the fixed-dose combination with no additional safety concerns outweighing the additional benefits of the fixed-dose combination from a parallel group comparison of the fixed-dose combination with the individual components at the same therapeutic doses.

For the purpose of the claim in second-line therapy, all studies were well-designed and well-conducted. Parallel group comparison of the combination with the individual components using the same therapeutic doses in the pivotal factorial study 301, demonstrated statistically significant superior efficacy of the combination. As well studies 302 and 303 demonstrated a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of either monotherapy.

The sponsor has provided some additional evidence of a supportive nature to substantiate a claim of maintenance of therapeutic effect of up to 44 weeks (open-label extension of study 301).

For the purpose of claiming efficacy as first-line therapy, the above guideline is not so helpful. It addresses necessary (but not sufficient) conditions to be satisfied by any application in which first-line therapy is claimed. There are two conditions, firstly demonstration that each component has a documented contribution within the (fixed) combination using sub-therapeutic doses and secondly

demonstration of a reduction of (dose-dependent) adverse drug reactions by the low-dose fixed combination as compared to the components in the lowest approved dosages. Apart from placebo, there was no testing of sub-therapeutic doses.

The guideline does not address what would constitute the sufficient rather than necessary conditions for the proof of a first-line claim. These would have to vary on a case-by-case basis and the Delegate raised particular points of concern regarding this application. There are also problems in the application of such particular guidelines when one looks at the actual evidence to support the claim of initial or first-line treatment. It also must be remembered that the guidelines are merely that, only guidelines.

Firstly, there are no data in the submission which actually compare directly the clinical efficacy and safety of the product given as a first-line treatment with those same parameters when the product is given in response to an add-on indication. The latter strategy which by and large is accepted as clinical best practice is the one of careful dose titration. It is a strategy which allows the clinician to gauge the efficacy and safety at each step. Very importantly such a strategy allows one to isolate effects such as the degree of efficacy and particular adverse events and assign attribution. There is no evidence in the submission which demonstrates that there is any significant difference in clinical outcome between patients treated via either of the two strategies. There are as well no clinical outcome data on morbidity or mortality.

In its pre-ACPM submission, the sponsor responded that these studies were not conducted as suggested by the Delegate. The sponsor, in consultation with the FDA, conducted Study 301 to demonstrate the safety and efficacy of the fixed-dose combination first line therapy in mild to severe hypertensive patients.

Secondly, there was only one study, the pivotal study 301, in which all patients randomized to the combination groups received the combination of olmesartan/amlodipine as the initial treatment without titration from monotherapy. This immediately gives rise to a question about the design of the study.

The sponsor disagreed with the Delegate's comment that the study design is flawed due to lack of dose titration. Period II of study 301 was designed in accordance to EU Regulatory Guidelines Section 7.2 "The Clinical Development of a Fixed Combination". This section required that "Preferentially, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their respective components and with placebo". It was not the intention to titrate patients to reach BP goal. The results from Period II demonstrated that each treatment group had a statistically and clinically significant mean reduction in SeDBP from baseline to Week 8 with LOCF ($p<0.0001$). Across all treatment groups, increases in dose were associated with progressively greater mean reduction in SeDBP and SeSBP. These results demonstrate that both components contribute to the efficacy of the combination.

There was no guard against treatment at an unnecessarily high dose. In the Delegate's opinion, because of the lack of any dose-titration, there is an important flaw in the study design. If, for example, a patient had been randomized to the olmesartan/amlodipine 20/5 mg group, there would have been still a reasonable chance that BP control would have been achieved with olmesartan/amlodipine 10/5 mg and even with amlodipine 5 mg monotherapy. In fact, given a 35.0% BP control rate with olmesartan/amlodipine 10/5 mg, there is up to a 35/42.5 (82.4%) chance that a patient in the olmesartan/amlodipine 20/5 mg group may have had his/her BP controlled with olmesartan/amlodipine 10/5 mg.

The sponsor commented that this calculation was incorrect. It would be more appropriate to use the probability graphs of patient reaching target BP goal based on their baseline BP when treated with different combination and mono-therapies to estimate the percentage of patients.

The Delegate noted that this risk of treatment with an unnecessarily high dose of the combination is clear when one looks at the four highest strength dosage combinations, 40/5,10/10, 20/10 & 40/10 mg. All of the latter had comparable proportions of patients who achieved their blood pressure goal. In fact the highest dosage strength, 40/10 mg, shared the lowest proportion of 49.1% with the 10/10 mg group, that is, one was just as likely to have achieved their blood pressure goal on a dose of 10/10 mg as on 40/10 mg. All of these examples go against the generally established and well accepted clinical principle of treating with the lowest possible dose(s).

The sponsor responded that unlike BP reduction, treatment to goal is a dichotomous evaluation based on criteria of 140/90 or 130/80. It depends upon baseline BP and the proportion of patients requiring a specific goal in that treatment arm. For these reasons, the proportion of patients reaching BP goal is not a good indication to establish dose-response (that is, between 40/10 and 10/10). The distribution of patients with different goals for each treatment arm and their baseline BP would impact the number of patients reaching goal in that arm. Looking at the therapeutic effect based on reduction in DBP and SBP clearly demonstrate a superior response at the highest 40/10 dose versus 10/10 in this study.

The Delegate noted that the sponsor's claim to first-line treatment is totally reliant upon a short-term, factorial study, 301, in which study there was an inherent risk of being exposed to an unnecessarily high dose. The other two studies, 302 and 303, do not support the claim to first-line treatment as both studies were add-on studies, that is, studies conducted according to what has been long recognised as best clinical practice (careful dose titration to the desired effect).

The sponsor responded that the safety and efficacy of fist-line treatment is supported by the results of both short-term Period II and long-term Period III of Study 301. Period II demonstrated the additive BP lowering effect for the combinations compared to their individual components in terms of efficacy. For safety, Period II also demonstrates the better toleration profile for combination therapy, particularly in relation to peripheral oedema. Addition of olmesartan reduced the incidence of oedema for amlodipine. Overall, the combination product was well tolerated: OM/AML combination was associated with a lower incidence of patients reporting adverse events (38.4 %) than either of its components administered as monotherapies (OM 43.4 % and AML 43.4 %) and placebo (56.8 %). The majority of adverse events were mild or moderate in severity, and the distribution by maximum severity was similar across all groups. The pattern for drug-related adverse events was similar, with OM/AML associated with lower incidences.

Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of various treatment combinations. All patients were switched to OM/AML 40/5 mg. Patients whose BP was not adequately controlled were titrated in an attempt to elucidate what may occur in clinical practice. If a patient experienced symptoms of hypotension or displayed intolerance to study medication, the patient was back-titrated. In addition, the open-label period of Study 303 (Period IV) was conducted in the same study design as Period III of Study 301.

The sponsor further noted that the percentage of total patients reaching BP target increased from 42.9% to 70.7% from week 0 to week 44. This pattern would be expected since patients who were not achieving target BP were up-titrated to a higher dose or receiving additional HCTZ. Similarly, the percentage of patients reaching BP goal in each treatment group also increased with time, as more patients who did not adequately respond were up titrated to another dosing regimen. These data also demonstrate that the efficacy of each dose regimen was maintained over the long term in patients remaining on that dose with no evidence of tolerance to long-term treatment. It is

important to note that by Week 44, only 31% of patients remained on AM/AML 40/5, while the remaining 79% were up-titrated.

The Delegate was concerned over the target group for initial or first-line therapy, namely "patients likely to need multiple antihypertensive agents to achieve their target BP goal". How is a clinician expected to make a judgement of who is likely to need multiple antihypertensive agents? Certainly there is no advice in the proposed PI on this matter. However, as pointed out above, there is crucially no guard against the possibility of treatment with unnecessarily high doses of the combination or even unnecessary treatment with the combination as opposed to a monotherapy.

The Delegate was also concerned over the broad approach of the second part of the indication sought, namely, "*treatment of hypertension in patients whose blood pressure is not adequately controlled on either angiotensin receptor blocker, ACE inhibitor or dihydropyridine calcium channel antagonist monotherapies*". There was no formal testing of this hypothesis in the clinical trial program presented in this application. The evidence was fragmentary because of its reliance on the literature. Olmesartan was only compared at one dosage strength, 20 mg and the comparisons with both valsartan and candesartan were potentially flawed In the opinion of the Delegate. All studies were short-term only. There was no comparison with eprosartan. There was no comparison with any of the more recent ACE inhibitors, the only comparisons being those with enalapril and captopril. There were no specific details of comparisons within the dihydropyridine calcium channel blocker class. Furthermore, in the proposed PI, there is no guidance offered on how switches from these other classes are to be made.

In summary, what has been offered in this submission is a collection of data which supports a second-line indication. However, there is no justification for first-line treatment in a patient group which is not clearly defined, that is, those likely to need multiple antihypertensive agents to achieve their target BP goal.

The sponsor discussed that for the clinician, using low or medium doses of complementary agents rather than maximum doses of single agents tends to improve blood pressure control more effectively and minimises adverse effects of individual agents. Some patients receive a mono-therapy which does not have a related fixed dose combination. The time required for a clinician to switch the patient to a similar monotherapy and then to prescribe the related fixed dose combination delays meeting blood pressure goals, and may lead to a reduction in compliance. Therefore, if agents within a class are known to have equipotent doses for lowering blood pressure, and are similar in efficacy and safety, switching of agents within a class to the fixed dose combination helps the patient reach their blood pressure goals faster.

The sponsor concluded that the data presented in the application provided evidence to support initial therapy in moderate to severe hypertensive patients (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) or hypertensive patients with high cardiovascular risk, who require a reduction in BP of at least 20/10 mmHg to reach goal. The sponsor further noted that acceptance of this indication would bring Australian practice in line with the recent change in the treatment paradigm from the more traditional titration approach of monotherapy to initiating patients with a fixed combination therapy. However, one must also consider the potential associated risk with initiating treatment with combination therapy for a proportion of patients who would have attained goal on monotherapy. By specifying moderate to severe patients, this would significantly reduce the proportion of patients likely to be controlled on monotherapy. The main concern of initiation with a combination therapy is unnecessary or excessive pharmacologic effect, most likely represented by hypotension or oedema. In Study 301, there was a low incidence of hypotension in patients requiring a BP reduction of ≥20/10 mmHg to reach their blood pressure goal. Five cases were reported; none of the events of hypotension was considered serious, and all patients recovered uneventfully. Current evidence favours initial combination treatement for a number of reasons: (i)

combination therapy results in greater BP reductions and gets more patients to target in a shorter time-frame, (ii) in high-risk patients, events can occur within a short time interval, thereby requiring prompt introduction of protective, risk minimisation interventions, (iii) protective effects of BP reduction are manifest shortly after initiation of the BP-lowering treatment, and (iv) initial combination treatment may be associated with an improvement in long-term compliance.

Switching patients within the ARBs and CCBs within the Therapeutic Group Premium is well accepted among the prescribers and the Pharmaceutical Benefits Pricing Authority. Considering the importance of reaching BP goals as soon as possible in reducing the potential cardiovascular risks in hypertensive patients, Schering-Plough believes there is adequate evidence to support the proposed indication for Sevikar for treatment of hypertension in patients whose BP is not adequately controlled on either ARBs or dihydropyridine CCB monotherapy. To make the switch easier for the prescriber, the sponsor would consider including information outlining the equipotent doses for all the ARBs and CCBs under the dosage section.

Safety

Studies found that olmesartan/amlodipine fixed-dose combination treatment of mild to moderately severe hypertension to be safe and well tolerated, up to a dose of 40/10 mg, with no unexpected adverse events or abnormalities. Sufficient evidence of long-term safety with respect to the current guideline was provided.

Summary overall

The Delegate stated that there is sufficient evidence of efficacy and safety in the submission to support the registration of the fixed-dose combination olmesartan/amlodipine tablets, 20/5, 20/10, 40/5 and 40/10 mg, as second-line therapy. In other words, there is sufficient evidence to support the standard indication:

Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

There is insufficient evidence to support any indication for initial or first-line treatment or any blanket indication for switching from other classes of anti-hypertensive medication.

There is insufficient evidence in the submission for the requested indications but instead the Delegate proposed to approve the submission for the indication above.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's responses to these documents, agreed with the Delegate's proposal. The ACPM recommended approval for the indication:

Treatment of hypertension.

Treatment should not be initiated with this fixed-dose combination.

In making this recommendation the ACPM concluded that the evidence of the safety and efficacy of the formulation and the dosage regimen for the proposed new indication has been sufficiently demonstrated. The ACPM advised that in the absence of data which directly compares the clinical efficacy and safety of the product given as a first-line treatment, with those same parameters when the product is given in response to an add-on indication, the inclusion of this indication is not supported. The requested indication for patients whose blood pressure is not adequately controlled on either angiotensin receptor blocker or dihydropyridine calcium channel antagonist monotherapies is not supported due to a lack of sufficient robust clinical data.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sevikar 20/5, Sevikar 20/10, Sevikar 40/5 and Sevikar 40/10 tablets containing olmesartan medoxomil / amlodipine besylate 20/5 mg, 20/10 mg, 40/5 mg and 40/10 mg for the indication:

Sevikar is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

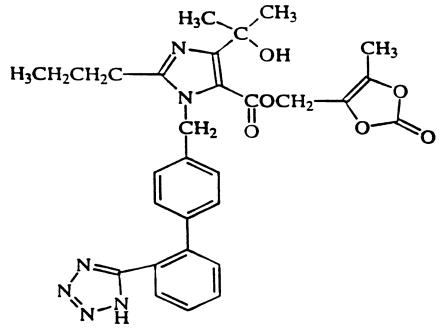
SEVIKAR®

(olmesartan medoxomil and amlodipine as besylate)

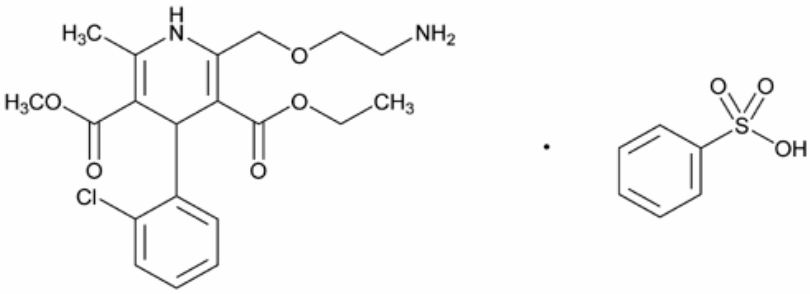
SEVIKAR 20/5
SEVIKAR 20/10
SEVIKAR 40/5
SEVIKAR 40/10

NAME OF THE MEDICINE

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. Its CAS number is 144689-63-4. Its structural formula is:



Amlodipine besylate 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. The CAS number is 111470-99-6 and its structural formula is:



DESCRIPTION

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

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).

PHARMACOLOGY

Pharmacodynamic properties

SEVIKAR is a combination of two antihypertensive drugs: olmesartan medoxomil, an angiotensin receptor blocker and amlodipine besylate, 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.

Pharmacokinetics

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 (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 and elimination

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 elimination

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 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

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 1 and 2). 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 1: 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 2: 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 3).

Table 3: 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 4).

Table 4: 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 5).

Table 5: 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 post dose. 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.

INDICATIONS

SEVIKAR is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

CONTRAINDICATIONS

SEVIKAR is contraindicated in:

- Patients who are hypersensitive to any component of the tablet or to dihydropyridines
- Pregnancy (see Precautions - Use in pregnancy)
- Patients with severe renal impairment (see Precautions - Renal impairment)
- Patients with severe hepatic impairment or biliary obstruction (see Precautions - Hepatic impairment)

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

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

PRECAUTIONS

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.

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 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 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).

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 Dosage and administration).

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. 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.

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.

In general, calcium channel blockers should be used with caution in patients with heart failure.

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).

Other

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

Use in 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 besylate 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.

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 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).

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).

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*).

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.

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

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) 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 Precautions).

Other drugs

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.

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 Precautions - Lithium). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other drugs

Drugs, which have been investigated in specific clinical studies in healthy volunteers, include warfarin, digoxin, an antacid (magnesium aluminium hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular olmesartan 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.

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.

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.

ADVERSE EFFECTS

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

Table 6 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 6: 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

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

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; 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

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 dues 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 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.

DOSAGE AND ADMINISTRATION

SEVIKAR is registered in four strengths: SEVIKAR 20/5 (olmesartan medoxomil 20 mg and amlodipine as besylate 5 mg); SEVIKAR 20/10 (olmesartan medoxomil 20 mg and amlodipine as besylate 10 mg); SEVIKAR 40/5 (olmesartan medoxomil 40 mg and amlodipine as besylate 5 mg); SEVIKAR 40/10 (olmesartan medoxomil 40 mg and amlodipine as besylate 10 mg). (See Presentation and storage conditions 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 Precautions – Intravascular volume depletion, and - Concomittant 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 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 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.

OVERDOSAGE

Symptoms

There is no experience of overdose 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

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 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 further advice on the management of an overdose contact the Poisons Information Centre.

PRESENTATION AND STORAGE CONDITIONS

SEVIKAR 20/5 contains 20 mg of olmesartan medoxomil and amlodipine 5 mg as besylate. It is a round tablet, approximately 6 mm in diameter, white in colour with C73 debossed on one side.

SEVIKAR 20/10 contains 20 mg of olmesartan medoxomil and amlodipine 10 mg as besylate. It 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 contains 40 mg of olmesartan medoxomil and amlodipine 5 mg as besylate. It is a round tablet, approximately 8 mm in diameter, cream in colour with C75 debossed on one side.

SEVIKAR 40/10 contains 40 mg of olmesartan medoxomil and amlodipine 10 mg as besylate. It is a round tablet, approximately 8 mm in diameter, brownish red in colour with C77 debossed on one side.

SEVIKAR 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

Schering-Plough Pty Limited
Level 4, 66 Waterloo Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF PREPARATION

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