Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Olmesartan medoxomil, Amlodipine (as besilate) and Hydrochlorothiazide

Proprietary Product Name: Sevikar HCT

Sponsor: Merck Sharp & Dohme Australia Pty Ltd

November 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New fixed dose combination of previously approved active ingredients
Decision:	Approved
Date of Decision:	11 September 2013
Active ingredients:	Olmesartan medoxomil, amlodipine (as besilate) and hydrochlorothiazide
Product Names:	Sevikar HCT 20/5/12.5, Sevikar HCT 40/10/25, Sevikar HCT 40/10/12.5, Sevikar HCT 40/5/12.5, Sevikar HCT 40/5/25
Sponsor's Name and Address:	Merck Sharp & Dohme (Australia) Pty Limited 54-68 Ferndell Street South Granville NSW 2142
Dose form:	Tablet
Strengths:	Sevikar HCT 20/5/12.5: Olmesartan medoxomil 20 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 12.5mg Sevikar HCT 40/10/25: Olmesartan medoxomil 40 mg, amlodipine (as besilate) 10 mg and hydrochlorothiazide 25 mg Sevikar HCT 40/10/12.5: Olmesartan medoxomil 40 mg, amlodipine (as besilate) 10 mg and hydrochlorothiazide 12.5mg Sevikar HCT 40/5/12.5: Olmesartan medoxomil 40 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 12.5 mg Sevikar HCT 40/5/25: Olmesartan medoxomil 40 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 25 mg.
Containers:	Blister pack
Pack sizes:	10, 30
Approved Therapeutic use:	Sevikar HCT is indicated for the treatment of hypertension, either as replacement for olmesartan medoxomil, amlodipine and hydrochlorothiazide being already taken as separate tablets or as add-on therapy where a patient's blood pressure is not controlled on a dual combination (see *Dosage and Administration*). This fixed dose combination is **not** indicated for initial therapy.
Route of administration:	Oral
Dosage (abbreviated):	The recommended dosage of Sevikar HCT is one tablet daily, with or without food. Treatment should not be initiated with this combination. The maximum dose is 40/10/25 mg once daily.
ARTG Numbers:	199006, 199007, 198998, 199005, 199000

Product background

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Limited (the sponsor) to register a new fixed dose combination (FDC) tablet containing olmesartan medoxomil (an angiotensin type 1 (AT_1) receptor antagonist), amlodipine besylate (a calcium channel blocker) and hydrochlorothiazide (a diuretic) in the following dosage strength combinations (olmesartan/amlodipine/hydrochlorothiazide in that order): 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 mg.

The proposed indication for Sevikar HCT is as follows:

> *Sevikar HCT is indicated for the treatment of hypertension.*
>
> *The fixed dose combination is not indicated for initial therapy.*

The proposed dosage instructions in the draft Product Information (PI) are as follows:

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

Replacement therapy

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

Add-on therapy

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

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

The individual active ingredients of Sevikar HCT are already registered as individual products or in dual combination products for the treatment of hypertension [Olmetec (olmesartan medoxomil), Olmetec Plus (olmesartan medoxomil + hydrochlorothiazide), Sevikar (olmesartan + amlodipine)].

The currently approved indication for Sevikar (fixed dose combination of olmesartan and amlodipine) is: *Sevikar is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination (see Dosage and Administration).*"

The approved indication for Olmetec Plus (fixed dose combination of olmesartan and hydrochlorothiazide) is: *Olmetec Plus is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination*.

Regulatory status

The products received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 September 2013.

At the time this application was considered by the TGA a similar application for the fixed dose combination had been approved in the US (September 2010), Switzerland (May

2011), The Netherlands (December 2010), the UK (December 2010) and a further 20 or more other countries in the European Union (EU, application via a de-centralised procedure).

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)

The structures of the three drug substances, olmesartan medoxomil (OM), amlodipine (as besilate) (AML) and hydrochlorothiazide (HCTZ) are presented below:

Figure 1. Structure of olmesartan medoxomil (OM).

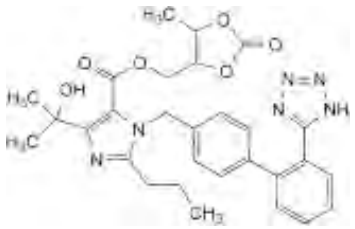


Figure 2. Structure of amlodipine besilate (AML).

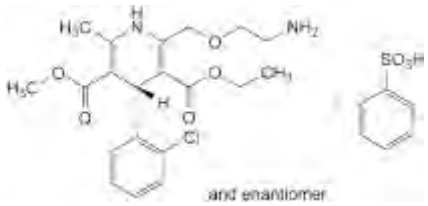
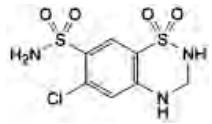


Figure 3. Structure of hydrochlorothiazide (HCTZ).



The three active pharmaceutical ingredients are manufactured and controlled in the same manner as the corresponding substances used in finished products currently registered to the sponsor.

Drug product

The proposed immediate-release tablets are distinguished by colour, size and debossing. The stability data provided supports a shelf life of 36 months when stored below 25°C in the proposed packaging.

Biopharmaceutics

Study CS 8635-A-E105 compared the bioequivalence and dose proportionality of the high (40/10/25 mg) and low (20/5/12.5 mg) dose tablet strengths versus two reference formulations. In Periods 1-3, subjects in a High Dose (HD) cohort received a single dose of

high dose Sevikar HCT, high dose OM+HCTZ (Benicar HCT identical to the Australian registered Olmetec Plus) tablet + high dose AML tablet (Antacal) and high dose OM+AML (Azor, quantitatively identical to the Australian registered Sevikar formulation) tablet + high dose HCTZ tablet. The Low Dose (LD) cohort received the corresponding low dose equivalents. In Period 4 subjects in the HD cohort received the low dose Sevikar HCT tablet strength and the LD cohort received the high dose Sevikar HCT to determine dose proportionality.

The high dose Sevikar HCT tablet was demonstrated to be bioequivalent to the reference formulations. The low dose Sevikar HCT tablet was similarly found to be bioequivalent to the reference formulations. The high and low strength Sevikar HCT tablets showed dose proportional pharmacokinetics (PK) for OM, AML and HCTZ.

Study CS 8635-A-U106 compared the effect of fed and fasted states for the proposed high dose Sevikar HCT tablet. Administration with food did not have a significant effect on the bioavailability of OM and AML. However administration with food decreased (23%) the peak exposure (C_{max}) of HCTZ without affecting the total extent of exposure (area under the concentration-time curve (AUC)). Administration with food decreased the time to peak exposure (T_{max}) of OM and HCTZ by 1 h and 0.5 h, respectively.

Questions in relation to biopharmaceutics data and the TGA evaluation of responses are shown under *Second round evaluation of clinical data submitted in response to questions* below. All matters raised were adequately addressed.

Advisory committee considerations

Not relevant.

Quality summary and conclusions

A number of issues were raised following the initial evaluation of this application and all issues were satisfactorily resolved.

There are no objections to registration of this product in respect of chemistry, manufacturing and controls.

Recommended revisions to the draft PI are beyond the scope of the AusPAR.

III. Nonclinical findings

Introduction

The nonclinical data bridging package consisted of an initial 28 day dose-range finding study in rats followed by a Good Laboratory Practice (GLP)-standard 3 month rat toxicity study (with accompanying toxicokinetics) which evaluated the potential for any new toxicities caused by concurrent oral administration of the triple combination of OM, HCTZ and AML. This was an appropriate strategy given the well characterised safety profile of the individual components as well as their previous nonclinical evaluation and subsequent extensive clinical use in various dual combinations (OM + HCTZ, OM + AML).

Pharmacokinetics

Olmesartan medoxomil + HCTZ treatment had no effect on the systemic exposure to AML (based on area under the concentration-time curve (AUC)). However, co-administration of

AML dose-dependently increased systemic exposure (AUC) to both OM and HCTZ in the 28 day and the 3-month studies in rats. This finding was previously noted for OM in the submission for the OM+AML combination (Sevikar) and was shown to be related to a significant drug-induced decrease in intestinal motility that results in markedly higher plasma levels of olmesartan associated with the exaggerated pharmacology of AML. While this effect is relevant to interpreting the present toxicological findings in rats, it does not appear to be clinically relevant as two clinical drug-drug interactions studies (CS-8635-A-U101 and CS-8635-U102) have shown that concomitant administration of OM, HCTZ and AML did not affect the pharmacokinetics (PK) of each compound at the doses tested (40/25/10 mg) under fasting conditions.

Toxicology

The ratio of individual components used in the rat toxicology combination studies with OM/HCTZ/AML (100/62.5/20 mg = ratio of 1.0/0.625/0.2) was similar to that proposed for clinical use (40/25/10 mg =1.0/0.625/0.25).

A preliminary 28-day dose range-finding study in rats (Study C-B394) at oral doses up to 100/62.5/20 mg OM/HCTZ/AML showed no mortality but elicited a suppression of body weight gain, increased urine volume, decreased red blood cell parameters, increased blood urea nitrogen level, regeneration of the renal tubules and thickening of the arterial wall in the kidney.

Similar dosages were subsequently used in the pivotal 3-month toxicity study where no novel toxicities were observed. Most of the changes seen reflect the 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) Decreased red blood cell parameters: reported previously in rats treated with angiotensin II receptor antagonists and appears to be a consequence of decreased erythropoietin production. (4) Increased stomach weight due to delayed OM/HCTZ evacuation due to the AML effect on intestinal smooth muscle.

Overall, it can be concluded that combined administration of OM, HCTZ and AML did not produce any novel toxicities or toxicologically significant synergistic effects.

Relative exposure

The relative exposures (compared with human exposure at the maximum clinical dose of 40/25/10 mg) attained for each component of the triple combination by the end of the 28 Day and 3 month rat studies are summarised in Table 1:

Table 1: Relative exposure to OM, HCTZ and AML attained in 28-day and 3-month rat studies

Dosing duration (sample time)	OM/HCTZ/AML (mg/kg/ day)	Analyte	Sex	$AUC_{0\text{-}24\ h}$ (ng.h/mL)	Exposure ratio#
28 days (day 28)	100/62.5/0	OM	M/F	15335/18356	2.4/2.9
	100/62.5/10	OM	M/F	26305/25879	4.1/4.0

Dosing duration (sample time)	OM/HCTZ/AML (mg/kg/ day)	Analyte	Sex	$AUC_{0\text{-}24\ h}$ (ng.h/mL)	Exposure ratio#
	100/62.5/20	OM	M/F	61728/45099	9.6/7.0
	50/31.25/20	OM	M/F	25841/36058	4.0/5.6
	100/62.5/0	HCTZ	M/F	37208/30382	33/27
	100/62.5/10	HCTZ	M/F	50969/50039	45/44
	100/62.5/20	HCTZ	M/F	68115/81546	60/72
	50/31.25/20	HCTZ	M/F	30577/49853	27/44
	100/62.5/10	AML	M/F	1010/1003	2.9/2.9
	100/62.5/20	AML	M/F	3633/3678	11/11
	50/31.25/20	AML	M/F	2914/4530	8.4/13
	0/0/20	AML	M/F	5335*/4654	15/13
3-month (Week 13)	100/62.5/0	OM	M/F	11600/15600	1.8/2.4
	100/62.5/10	OM	M/F	48700/31700	7.6/4.9
	100/62.5/20	OM	M/F	65800/34800	10/5.4
	30/18.75/20	OM	M/F	25300/12500	4.0/2.0
	100/62.5/0	HCTZ	M/F	27800/27800	25/25
	100/62.5/10	HCTZ	M/F	112000/57800	99/51
	100/62.5/20	HCTZ	M/F	108000/61100	95/54
	30/18.75/20	HCTZ	M/F	17100/13100	15/12
	100/62.5/10	AML	M/F	2090/1390	6.0/4.0
	100/62.5/20	AML	M/F	5870/3650	17/11
	30/18.75/20	AML	M/F	5440/4640	16/13
	0/0/20	AML	M/F	6520/6350	19/18

*n=2; # Animal plasma $AUC_{0\text{–}24\ h}$ values were divided by the geometric mean human plasma $AUC_{0\text{–last}}$ values derived from Study CS8635-A-U103 where the triple combination formulation (OM/HCTZ/AML) was given at 40/25/10 mg : OM: 6405 ng.h/mL; HCTZ: 1132 ng.h/mL; AML: 346 ng.h/mL.

Table 1 shows that exposures to OM, HCTZ and AML in both toxicity studies were higher than that anticipated clinically at the maximum recommended human dose in all dose

groups. In the main 3-month study the maximum exposure margins attained were about 10 times (OM), 100 times (HCTZ) and 20 times (AML) the expected maximum clinical exposure to each component.

Genotoxicity, Carcinogenicity, and Reproductive and Developmental toxicity

No studies were submitted by the sponsor under these headings, which is acceptable and consistent with International Conference on Harmonization (ICH) *Guideline on the non-clinical development of fixed combinations of medicinal products* (EMEA/CHMP/SWP/258498/2005) regarding fixed dose combinations of previously approved components. All three 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 draft PI, Sevikar HCT should not be used during pregnancy, consistent with the known effects of angiotensin receptor blockers in the second and third trimesters of pregnancy.

Nonclinical conclusions and recommendation

- No significant novel toxicities were noted for the OM + AML + HCTZ combination in a well-conducted, GLP-compliant, 13-week oral toxicology study in rats. The changes observed in the combination groups were consistent with the pharmacology attributable to its individual components.
- The toxicities observed have been described previously for these drugs or for drugs of the same class and reflect target organ toxicities that can be monitored in the clinic. As all three active compounds have been approved and on the market for some years and as there are 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 are no objections to the registration of Sevikar HCT tablets for the treatment of hypertension.

Recommended revisions to the nonclinical statements in the proposed PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The current approved PI for Sevikar (OM + AML) includes a statement that if blood pressure (BP) lowering is insufficient then HCTZ addition is recommended. The proposed triple FDC has been developed to offer treatment in a single tablet where a patient requires all three agents to adequately reduce BP. The sponsor's justification for the product is that *"A fixed-dose triple combination treatment of OM + AML + HCTZ will not only help more subjects achieve blood pressure goals, but will provide a more convenient way of administering an antihypertensive regimen".* The sponsor also states that *"fixed-dose combinations, particularly for subjects with more severe hypertension, may improve the control of hypertension by enhancing compliance, by achieving blood pressure goals rapidly, and by reducing physician inertia in prescribing adequate antihypertensive therapy."*

Scope of the clinical dossier

The submission contained the following clinical information:

- Six clinical pharmacology studies including: four bioavailability studies (CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U101); one bioequivalence study (CS8635-A-U105) and one food effect study (CS8635-A-U106). All these studies provided PK data and none provided pharmacodynamic (PD) data.
- One population PK analysis.
- One pivotal Phase III efficacy and safety study (Study CS8635-A-U301).
- One Phase IV open label study (Study SP-OLM-03-05).
- Two open label extension studies which had been previously evaluated by the TGA (Studies CS8663-A-U301 and CS8663-A-E303).
- An *Integrated Summary of Safety*, literature references and study data listings.

Guidance

There was no formal pre-submission meeting between the sponsor and the TGA in relation to this dossier. The sponsor stated in the clinical overview that a meeting was held with the US FDA and it was agreed that a single pivotal Phase III trial demonstrating superiority in BP lowering of the triple combination over the highest dosage dual combination (each of the three dual combinations) was sufficient, pending review, to support registration. There was no statement from the sponsor in the dossier regarding adherence to relevant clinical development guidelines.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

In each clinical study report (CSR), the sponsor declared that studies were conducted according to Good Clinical Practice guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 shows the studies relating to each PK topic.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of the study
PK in healthy adults	*General PK*		
	Single dose	N/A	
	Multi-dose	N/A	
	Bioequivalence†		

PK topic	Subtopic	Study ID	Primary aim of the study
	Single dose	CS8635-A-E105	Compare the PK of MIF versus the two reference clinical formulations at 2 dose strengths.
		CS8635-A-U101	BA of Benicar HCT and Norvasc when given together and when administered alone.
		CS8635-A-U102	BA of CS-8663 and HCT when given together and when administered alone.
		CS8635-A-U103	BA of CS-8635 (Pilot Formulation A) and of a two-tablet regimen (Benicar HCT plus Antacal)
		CS8635-A-U104	BA of CS-8635 (Pilot Formulation B) and of a two-tablet regimen (Benicar HCT plus Antacal)
	Multi-dose	N/A	
	Food effect	CS8635-A-U106	PK CS-8635 MIF [0/10/25 mg under fed and fasting conditions
PK in Target population	Single dose	N/A	
	Multi-dose	N/A	
PK in Special populations	Hepatic impairment	N/A	
	Renal impairment	N/A	
	Neonates/ infants/children /adolescents	N/A	
	Elderly	N/A	
	Other special populations	N/A	
Genetic/ gender-related PK	Males versus females	N/A	
	other genetic variable	N/A	
PK interactions	Olmesartan/ amlodipine/HCT	CS8635-A-U101 CS8635-A-U102	PK interaction between 3 active components

PK topic	Subtopic	Study ID	Primary aim of the study
Population PK analyses	Target population	CS8635-A-U301	

BA: bioavailability; CS-8635: Sevikar HCT; CS-8663: 40 mg OM + 10 mg AML (Sevikar); Benicar HCT: OM+HCTZ; Antacal: AML; Azor: OM + AML; Norvasc: AML. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's overall summary and conclusions on pharmacokinetics

- Other than bioequivalence/bioavailability and food studies the sponsor provides no new information on the PK of Sevikar HCT or its individual active components.
- Following administration of a single dose of the Market Image Formulation (MIF) of Sevikar HCT (40 mg OM + 10 mg AML + 25 mg HCTZ) to healthy subjects the C_{max} and AUC over time zero to infinity (AUC_{inf}) of the OM component was 908 ng/mL and 6277 ng.h/mL, respectively, and the T_{max} and $t_{½}$ were 1.5 h and 17.4 h respectively. For the AML component, the corresponding PK parameters were 7.5 ng/mL, 372 ng.h/mL, 7 h and 41.5 h, respectively, and for HCTZ component the values were 193 ng/mL, 1223 ng.h/mL, 1.5 h and 10.2 h, respectively.
- Population PK modelling indicated that:
  - the PK of OM was adequately characterised by a two-compartmental model with first-order absorption and time lag; creatinine clearance was a significant predictor of the apparent oral clearance;
  - the PK of AML was adequately characterised by a two-compartmental model with first-order absorption and a time lag; age was a significant predictor of the apparent oral clearance;
  - the PK of HCTZ was adequately characterised by a two-compartmental model with first-order absorption and a time lag; sex, age and creatinine clearance were significant predictors of the apparent oral clearance.
- No studies examined the bioequivalence of the MIF of Sevikar HCT and individual doses of the three active components. No formal justification for a biowaiver has been provided by the sponsor.
- The MIF and two reference clinical formulations (Benicar HCT + Antacal and Azor + HCTZ) were bioequivalent at 2 dose strengths (40/10/25 mg and 20/5/12.5 mg OM/AML/HCTZ).
- The three active components of the low dose MIF (20/5/12.5 mg OM/AML/HCTZ) and the high dose MIF (40/10/25 mg OM/AML/HCTZ) were bioequivalent when dose normalised indicating dose proportional PKs for the two MIF dosage strengths.
- Benicar HCT + Norvasc was bioequivalent with Benicar HCT in regard to OM and HCTZ AUC and C_{max}, and Benicar HCT + Norvasc was bioequivalent with Norvasc in terms of AML AUC and C_{max}.
- CS-8663 (OM + AML) + HCTZ was bioequivalent with CS-8663 in regards to OM and AML AUC and C_{max}, and CS-8663 + HCTZ was bioequivalent with HCTZ in terms of HCTZ AUC and C_{max}.

- Two pilot formulations (Formulation A and B) of the fixed dose triple combination were bioequivalent with a two-tablet regimen (Benicar HCT plus Antacal) in regard to the AUC and C_{max} of the three active components.
- The PK of the 3 active components of Sevikar HCT following a single dose were bioequivalent in regards to OM and AML AUC and C_{max} in fasted and fed subjects. By contrast, although the AUC of HCTZ was bioequivalent between the two groups, the C_{max} of HCTZ was not bioequivalent and was approximately 23% lower in fed subjects. Given the bioequivalence result on AUC, this food effect on C_{max} is not considered to be clinically relevant.
- Population PK modelling indicated that being of Black race was a clinically significant covariate which decreased the maximal possible effect on BP of OM without influencing PK parameters
- There was no drug-drug interaction between the active components of the triple combination therapy.
- It is not known whether the AML and HCTZ forms used in the bioequivalence/bioavailability studies are comprised of similar constituents and have similar dissolution profiles to the forms of the drugs marketed in Australia. Therefore, it could be argued that the bioequivalence/bioavailability testing program described in the evaluation materials may have little relevance for the Australian market. The sponsor was requested to provide further information on these issues (see below under *Second round evaluation of clinical data submitted in response to questions*).

Pharmacodynamics

Mechanism of action

Olmesartan medoxomil

Olmesartan medoxomil (the prodrug form of active olmesartan) is an orally active angiotensin II (AT_1) receptor antagonist intended for use in treating hypertension. Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is independent of the pathways for angiotensin II synthesis. With chronic daily oral administration, antihypertensive effectiveness is maintained for at least 24 h.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group and 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. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in BP. As a result, following administration of therapeutic doses to patients with hypertension, AML produces vasodilation resulting in a reduction of supine and standing BPs. With chronic daily oral administration, antihypertensive effectiveness is maintained for at least 24 h.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of HCTZ reduces plasma volume with consequent increases in plasma renin activity, increases in aldosterone

secretion, increases in urinary potassium loss and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with this diuretic.

Studies providing pharmacodynamic data

Other than the population PK study no new studies were provided in the evaluation materials that specifically examined the PD activity of the triple formulation.

Evaluator's overall conclusions on pharmacodynamics

Population PK modelling indicated:

- the effects of OM and AML on trough seated diastolic blood pressure (sDBP) and trough seated systolic blood pressure (sSBP) were described by an E_{max} (concentration-response) model, whereas the drug effect of HCTZ exposure was described by a linear model;
- the BP lowering effects of OM, AML and HCTZ in monotherapy, dual combination therapy and triple combination therapy were well characterised by a model composed of the sum of the individual effects and interaction among the components;
- the baseline trough sDBP and sSBP were significant covariates, with more BP lowering effect associated with higher baseline BP; and
- the BP lowering effects of the OM + AML + HCTZ triple combination were superior to the effects seen with mono and dual therapies of OM, AML and HCTZ.

Efficacy

Dosage selection for the pivotal studies

The doses proposed in the FDC product are the same as those currently available in the respective mono-therapies and dual-therapies, that is, 20 mg and 40 mg for OM, 5 mg and 10 mg for AML and 12.5 mg and 25 mg for HCTZ.

Studies providing efficacy data

The following studies were provided:

- Pivotal Phase III efficacy and safety Study CS8635-A-U301.

The pivotal Study CS8635-A-U301 was a Phase III, multicentre, randomised, parallel group study in adults aged ≥18 years with hypertension. There were three periods: Period 1 was a washout (3 weeks maximum duration) to determine eligibility; Period 2 was a 12 week double-blind treatment period; and Period 3 was a 40 week open label treatment period and a 2 week follow up.

The primary objective was to determine if the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg had a clinically significant benefit versus the respective dual therapy components (OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, AML 10 mg + HCTZ 25 mg) in controlling BP after 12 weeks of treatment.

- Two open label extension studies, part of which had been previously evaluated by the TGA (Studies CS8663-A-U301 and CS8663-A-E303).

The dossier included further data from two clinical study reports (CS8663-A-U301 and CS8663-A-E303) which had previously been evaluated as part of the submission for Sevikar (olmesartan/amlodipine).

Study CS8663-A-U301 was a randomised, factorial, 8 week study evaluating the efficacy and safety of co-administered OM and AML compared to monotherapy in 1400 adults with mild to severe hypertension (mean baseline SBP/DBP of 163.6/101.5 mmHg). The dossier included the CSR for Period III of the trial which was an open label, 44 week (week 8 to 52) extension study.

Study CS8663-A-E303 was a Phase III, randomised, 52 week study of add-on OM in 755 adult subjects with moderate to severe hypertension inadequately controlled on AML 5 mg. The first three periods of the study were 8 weeks each and were: open label AML; double blind fixed dose; and double blind with dose titration. The dossier included the CSR for Period IV of this study which covered a 28 week open label extension (weeks 24 to 52) in 692 subjects. In this Period, subjects received OM 40 mg and AML 5 mg which could be uptitrated to AML 10 mg. After this, HCTZ 12.5 mg and then 25 mg could be added if required.

- Phase IV open label Study SP-OLM-03-05.

This was a 22 week, Phase IV, open label, non-comparative, multicentre study of OM and sequential add-on treatment of HCTZ and AML in 694 subjects with mild to moderate hypertension.

The primary objective was to evaluate the rate of subjects treated to target (STTT) overall and at each combination treatment step. The target BP (at trough) was mean sSBP (msSBP) ≤130 mmHg and mean sDBP (msDBP) ≤85 mmHg for non-diabetics and msSBP <130 mmHg and msDBP <80 mmHg in diabetics.

Evaluator's summary and conclusions on clinical efficacy for hypertension

The efficacy of the triple combination was based on one large pivotal Study CS8635-A-U301. This was a Phase III, multicentre, randomised, parallel group study in 2492 adult (≥ 18 years) subjects with hypertension, 627 of whom received the triple combination. After a run-in of at least 2 weeks on high dose dual therapy, subjects remained on dual therapy or were titrated to the maximal dose triple therapy.

The triple combination dose of OM 40/HCTZ 25 + AML 10 was found to significantly reduce sDBP and msSBP to a greater level than any of the three dual therapy combinations. The addition of the HCTZ 25 mg component to the dual therapy contributed a BP reduction of 7.1/3.8 mmHg, AML 10 mg contributed 7.4/4.9 mmHg and OM 0 mg contributed 9.6/6.7 mmHg. Target BP attainment rates at week 12 were significantly greater with triple therapy than dual therapy (64.3% versus 34.9-46.6%).

The 24 h ambulatory BP monitoring (ABPM) sub-study in 440 subjects confirmed the difference between triple and dual therapy over the 24 h dosing interval. Results were consistent across subgroups of age, gender, race and hypertension severity.

In this study there were too few subjects over 75 years or with renal impairment to allow meaningful comparisons. There were also very few Asian subjects. Triple therapy treatment in the study was achieved by using a combination of Benicar HCT (OM/HTCZ 40/25) with Antacal 10 mg (AML) so it was important to see that bioequivalence of these products to the proposed FDC was demonstrated.

The study was reported to have a 40 week open label Period III (weeks 12 to 52), however the data were not provided in the dossier. Given the first part of the study was completed in 2009, these should be available and are necessary to provide data on the persistence of efficacy and tolerance.

The pivotal study was a head to head comparison of triple versus dual therapy in subjects with moderate hypertension. It did not directly assess the efficacy of triple therapy in subjects who had not adequately responded to dual therapy, although this was done on an exploratory basis and was suggestive of a positive response.

Some supportive efficacy data was provided in Study SP-OLM-03-05. This was an open label, non-comparative Phase IV study in 694 adults with mild to moderate hypertension. Subjects received a stepped treatment algorithm of OM 20 mg, HCTZ (12.5 and 25 mg) and AML (5 and 10 mg). Using this treatment sequence a SBP/DBP target of ≤ 130/85 mmHg (or <130/80 mmHg in diabetics) could be achieved in 72% of subjects with a mean overall BP reduction of 30/16 mmHg.

The dossier also included clinical study reports of the extension arms of Studies CS8663-A-U301 and CS8663-A-E303. These studies had previously been evaluated by the TGA (in 2009) for the Sevikar (OM + AML) submission. The data showed that efficacy of dose regimens was maintained over the long term (to 52 weeks).

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

In the pivotal efficacy study (CS8635-A-U301) the following safety data were collected:

- General adverse events (AEs) were assessed at each visit.
- Adverse events of interest included oedema, headache, hypotension, dizziness and vertigo, syncope, renal impairment, hepatic related events, hyper- and hypokalaemia, glycaemic control related events, falls, gout and hyperuricaemia.
- Laboratory tests, including chemistry, haematology and urinalysis, were performed at screening, Day 1 and then Week 12, 20 and 52.
- Vital signs, electrocardiograms (ECGs), and physical examination.

The non-pivotal efficacy studies provided safety data, as follows:

- Studies CS8663-A-U301 and CS8663-A-E303 provided data on AEs, specific AEs and clinical laboratory assessments. Subjects entering the open label periods of these studies were included in the integrated analysis of safety of the Phase III open label cohort.
- Study SP-OLM-03-05 provided data on AEs and clinical laboratory assessments. Data were divided into three safety sets: Safety set 1 was subjects who received OM; Safety set 2 was those who received HTCZ; and Safety set 3 was those who received AML at least once (that is, triple therapy).
- The clinical pharmacology Studies CS8635-A-U101, -U102, -U103, -U104, -E105 and -U106 provided data on AEs. Data were included in an integrated analysis of safety for the Phase I cohort.

The Safety set was defined as all randomised subjects who received at least one dose of study medication and had at least one post dose safety assessment. In the pivotal study, the primary assessment of AEs was on the Safety set 2 from Day 1 to Week 12. The Safety set 2 was defined as the subjects who took at least one dose of study medication at or beyond the Week 4 visit when treatment with triple therapy commenced.

Data from the 40 week open label extension of the pivotal study was not included in the dossier.

Patient exposure

In the pivotal Study Safety set 2, there were 574 subjects exposed to triple therapy for a mean duration of 53.6 days. Due to the study design, the mean duration of exposure to dual therapy was longer (82.7 to 83.0 days).

In the Phase III open label cohort (uncontrolled extensions of Studies CS6883-A-U301 and -E303), there were 829 subjects who received OM 40 mg /AML 10 mg/HTCZ 12.5 mg for a mean duration of 111.6 days and 468 who received OM 40 mg/AML 10 mg/HTCZ 25 mg for mean duration of 175.0 days. The mean exposure to dual therapy AML 10 mg/HCTZ 25 mg was 79.5-100.9 days. Due to the difference in duration of exposure, comparisons between triple and dual therapy group rates are not directly possible.

In the phase IV study, 294 subjects received triple combination (OM 20 mg/AML 10 mg/HTCZ 12.5 mg or OM 20 mg/AML 10 mg/HTCZ 25 mg for a mean duration of 45.6 days.

Post-marketing experience

Data from the Phase IV study has been included. No other post-marketing data was submitted.

Evaluator's overall conclusions on clinical safety

The pivotal Study CS8635-A-U301 provided the primary safety data in which there were 574 subjects exposed to triple therapy for a mean duration of 53.6 days. This mean exposure to triple combination included a titration period which was slightly shorter than the dual therapy periods of around 83 days. Exposure was at the highest dose of the triple therapy (OM/AML/HCTZ 40/10/25 mg). The placebo group in the pivotal study was too small (n=36) to provide data for safety comparisons. The open label cohort provided long term data in which there were 829 subjects who received OM 40 mg/AML 10 mg/HTCZ 12.5 mg for a mean duration of 111.6 days and 468 who received OM 40 mg/AML 10 mg/HTCZ 25 mg for mean duration of 175.0 days.

Overall, the safety risks seen were in line with what is known for the individual components and there were no new safety signals with co-administration of the three components.

The rate of treatment emergent adverse events (TEAEs) was similar between triple and dual therapy groups (58.4% versus 51.7-58.9%) and events were generally mild (31.9% versus 26.8-30.5%) or moderate (22.3% versus 20.8-26.6%) in severity. Severe TEAEs were less frequent and rates were in line with dual therapy (4.2% versus 2.9-4.0%).

There were two deaths in the safety dataset; one from "alcohol poisoning" and the other from a gunshot wound. Both subjects were on dual therapy. Serious adverse event (SAE) rates were similar to dual therapy in the short term (1.6% versus 1.3-1.8%) and rates remained low in the longer term population (1.8% and 3.8% for OM 40/AML 10/HCTZ 12.5 mg and OM 40/AML 10/HCTZ 25 mg, respectively). The SAEs which resulted in discontinuation in subjects treated with triple therapy included: hepatic malignant neoplasm, psychotic disorder, chest pain, dizziness, small intestine obstruction and coronary artery disease.

Discontinuation of treatment due to AEs occurred in 7.7% of subjects in the pivotal study which was marginally higher than dual therapy (3.5-7.2%). The most frequent TEAEs leading to discontinuation were dizziness (1.0% versus 0.2-0.3%), peripheral oedema (0.9% versus 0.2% both) and hypotension (0.7% versus 0-0.3%). In the longer term, the discontinuation rate due to AEs was slighter higher with the maximal dose compared to

OM 40/AML 10/HCTZ 12.5 mg (2.5% versus 1.3%). The rate of treatment-related TEAEs was again no greater than dual therapy (28.2% versus 20.9-29.7%).

The most common TEAEs in the triple compared to dual therapy groups were dizziness/vertigo (11.3% versus 3.4-10.7%), oedema (7.7% versus 1.6-9.8%), headache (6.4% versus 6.0-7.0%) and fatigue (4.2% versus 5.3-6.5%). Oedema is known to occur with AML and was also notable in subjects with this as one of the therapy components. While the rate of dizziness/vertigo was similar to OM 40/HCTZ 25 (11.3% versus 10.7%) it was more frequent than the other dual therapies (3.4-5.5%). The rates of hypotension (2.1% versus 0-0.7%) and syncope (1.0% versus 0-0.5%) were higher with triple than dual therapy.

There was a risk of high potassium with triple therapy, which was not higher than OM 40 mg/HCTZ (5.9% versus 7.6%), although the risk of TEAEs of hyperkalaemia was greater than with dual therapy (0.9% versus 0.3-0.5%). The rate of low potassium was similar to OM 40 mg/HCTZ (2.2% versus 2.4) and less than with AML 10/HCTZ 25 mg (9.8%)

The rates of increased creatinine (6.4%) and creatinine clearance ≤60 mL/min (5.4%) were not higher with triple therapy than with OM 40/ HCTZ 25 mg (7.1% and 6.6%, respectively). There was however an increased risk of renal impairment TEAEs with triple therapy (2.1% versus 0.2-1.3%). The rates of glycaemic control events and gout, hyperuricaemia and increased uric acid events were no greater with the triple therapy than other groups.

Electrocardiogram findings were unremarkable. There were small increases in liver function with marked elevation of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin occurring in 1.3%, 2.7% and 0.2% of subjects respectively, though this was no greater than with dual therapy.

There were no new safety signals across subgroups of gender, race (Blacks), ethnicity (Hispanics), diabetes, hypertension stage and severity, and body mass index (BMI). In subjects aged ≥65 years the rate of SAEs was higher in those treated with triple therapy (5.1% versus 1.6-3.4%) although discontinuation rate due to TEAEs was not (4.2% versus 0.9-4.5%). The number of subjects aged ≥75 years was too small to draw conclusions in this age group. Compared to those aged <65 years, the elderly had higher risks of oedema, dizziness, renal impairment AEs and hypotension when treated with triple therapy.

Treatment withdrawal effects were not studied with the triple combination. As such effects are not associated with the component products this would not be an expected issue with the triple therapy.

Safety data from the 40 week extension of the pivotal study were not included in the dossier and need to be submitted.

First round benefit-risk assessment

First round assessment of benefits

The benefits of OM/AML/HCTZ in the proposed usage are:

- A clinically meaningful and statistically significant antihypertensive effect together with greater BP control rates than the respective dual therapies.
- The addition of the HCTZ 25 mg component to the dual therapy contributed a BP reduction of 7.1/3.8 mmHg, AML 10 mg contributed 7.4/4.9 mmHg and OM 40 mg contributed 9.6/6.7 mmHg.

- The antihypertensive effect was maintained over 24 h on ABPM, and appears to be sustained over 6 months of treatment with no evidence of tolerance, although the long term data from Study CS8635-A-U301 need to be submitted to confirm this.
- Efficacy was seen in patients with mild to severe hypertension and was also seen across subgroups of age, gender, race, body mass index (BMI), and diabetes.
- The treatment is a once a day dosing of a single tablet which may assist in patient compliance and improved treatment acceptance. The modes of action of the three treatments are complementary.
- An acceptable safety profile similar to the component mono-therapies with no new safety signals identified.
- The MIF was bioequivalent with the combination of Benicar HCT (OM/HCTZ) and Antacal (AML) and the combination of Azor (OM/AML) and HTCZ for both the highest 40/10/25 mg and lowest 20/5/12.5 mg doses. Benicar HCT and Azor have the same formulations as the Australian products Olmetec Plus and Sevikar, respectively
- There were no drug interactions between the active components of the triple combination.

First round assessment of risks

The risks of OM/AML/HCTZ in the proposed usage are:

- The BP lowering effects of the triple combination have only been studied with the maximum dose and not the 4 lower proposed doses.
- Greater risks of hypotension, dizziness/vertigo, and syncope than with dual therapy and a resultant slightly higher rate of discontinuation due to AEs.
- Renal impairment AEs which occurred at a higher rate than with dual therapy. The therapy should be used with caution in patients with renal impairment and is contraindicated in severe renal impairment.
- Other frequent events were oedema, headache, nausea, fatigue, hyperkalaemia and hypokaleamia. Oedema is associated with AML 10 mg and was not greater than with AML 10 mg/HCTZ 25 mg.
- The known risks to the fetus of agents acting on the renin-angiotensin system and thiazides are known to be excreted in breast milk.
- There are currently no morbidity or mortality outcome data available for OM.
- There were limited data on subjects aged 75 years and over.
- There is a lack of efficacy and safety data in patients with high cardiovascular risk as those with severe hepatic and renal impairment, heart failure, a recent history of myocardial infarction or cerebrovascular disorders were excluded from the clinical program.
- Numerous possible drug interactions.
- There are no data addressing the comparability of the mono-therapies of AML and HCTZ used in the bioequivalence/bioavailability program with those available on the Australian market.
- There are no bioequivalence data between the three single components and the MIF triple combination.
- The bioequivalence of the middle three doses (OM/AML/HCTZ 40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg) of the triple combination has not been evaluated.

First round assessment of benefit-risk balance

It has been reported that many patients with hypertension will not achieve their target BP with monotherapy and may require a combination of two or more agents. Given patients in this group may require three therapies there is an evident clinical place for a combination tablet to increase patient acceptance and compliance. Amlodipine and HCTZ are well known products with established safety profiles and have complementary actions with OM so the combination is a rational choice for three agents which are currently registered in Australia.

The clinical development program was conducted in line with recommendations for fixed dose combinations (CHMP 2009[1]). The pivotal study's design and BP assessment methods (at trough and with standardised methods and conditions) were also in line with European Medicines Agency (EMA) guidelines (EMA 2010[2]). The study used diastolic BP as the primary endpoint and so it was important to see a statistically significant and clinically beneficial effect on systolic BP as the latter is the preferred primary variable (EMA 2010).

As is frequently the case with this type of clinical trial, patients with more severe co-morbidities were excluded (for example, recent myocardial infarction, New York Heart Association (NYHA) class ≥ III cardiac failure, creatinine clearance < 30 mL/min). In addition, there were few subjects 75 years or older. These issues need to be adequately covered in the PI. Rebound hypertension was not assessed, although it is not anticipated to be an issue as withdrawal effects are not mentioned in the respective monotherapy PI documents.

The maximal dose triple combination (OM 40 mg + HCTZ 25 mg + AML 10 mg) was found to significantly reduce msDBP and msSBP to a greater level than any of the three dual therapy combinations without compromising safety. The safety profile from the pivotal trial and the long term safety cohort was as would be expected from the mono-therapies and no new safety signals were identified. The triple therapy did result in an increased risk of renal impairment AEs as well as of dizziness, hypotension and syncope. These risks have been adequately covered in the PI and Consumer Medicine Information (CMI). Other risks such as the known fetal and neonatal risks are also clearly specified and the product is contraindicated in pregnancy and during lactation.

The pivotal Study CS8635-A-U301was reported to have a 40 week open label Period III (weeks 12 to 52), however the data were not provided in the dossier. Given the first part of the study was completed in 2009, these should be available and are necessary to provide data on the persistence of efficacy and tolerance as well as very relevant long term safety data.

The currently proposed indication (*Sevikar HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy*) is too broad and implies that the triple therapy could be used as a second line treatment for hypertension. It is acknowledged that patients with severe hypertension may require triple therapy to reach their BP goals. Nevertheless, in line with hypertension treatment guidelines (NHF 2010[3], NICE 2011[4]), the evaluator recommends that therapy should be via a stepwise addition of agents and treatment with two agents used prior to the addition

[1] EMA, 2009. *Guideline on clinical development of fixed combination medicinal products.* CHMP/EWP/240/95 Rev 1.
[2] EMA 2010. *Guideline on clinical investigation of medicinal products in the treatment of hypertension*. EMA/238/1995/Rev.3.
[3] NHF (2010). National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Updated December 2010.
[4] NICE (2011). Hypertension: Clinical management of primary hypertension in adults. Clinical Guideline CG127. August 2011.

of a third. Therefore, triple therapy should be reserved for third line treatment. Consequently, there are two appropriate situations where a triple therapy could be used: substitution and add-on therapy. Substitution should be dose for dose in those adequately controlled on the three individual therapies. Add-on therapy should be when an additional therapy is being considered in those whose BP is not adequately controlled on dual therapy.

The clinical development program was based on one pivotal study. This study demonstrated superiority in BP reduction of the triple therapy compared to the three possible dual therapies in patients with moderate to severe hypertension. While this study provided some evidence of efficacy as add-on therapy in patients not adequately controlled on dual therapy, this was in an exploratory subgroup analysis. Guidance documents for products in the treatment of hypertension (EMA 2010) clearly state that for development of second or third line therapy *"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"*. That is, in order to support an indication of add-on therapy, studies are required *"to demonstrate 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 one or more of the mono-components"* together with safety concerns that *"do not outweigh the additional benefit of the combination".* The pivotal study did not have this design and the dossier did not include any specific add-on therapy studies. Consequently, the evaluator cannot support an indication for add-on therapy and only recommends use for therapy substitution.

In the pivotal trial, the triple combination was achieved using Benicar HCT (OM/HCTZ) and Antacal (AML), therefore the establishment of bioequivalence to the MIF is critical. This was demonstrated for the highest (40/10/25 mg) and lowest (20/5/12.5 mg) doses. Bioequivalence was also demonstrated with another dual therapy Azor (OM/AML) combined with HCTZ for the lowest and highest dose. The products Benicar HCT and Azor are the same formulations as the products Olmetec Plus and Sevikar, which are available in Australia. It is unknown, however, whether the AML and HCTZ forms used in the bioequivalence studies are comprised of similar constituents and whether they have similar dissolution profiles as those available on the Australian market. As such, prior to any approval this issue would need to be satisfactorily addressed. Assuming this is achieved, then the bioequivalence data would allow substitution of the dual plus single component therapy at the lowest and highest dose of the triple combination. By contrast, there were no data provided or biowavers requested for bioequivalence of the middle three proposed strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg). As a result, the evaluator cannot support the registration of these three middle doses. Likewise, without data that demonstrate bioequivalence between the three mono-components and the MIF triple combination, the evaluator does not support direct substitution between single components and the triple combination.

The evaluator proposes the following indication:

> *Sevikar HCT is only indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) and a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.*

There are five strengths proposed: 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg and 40/10/25 mg. The missing combinations are the OM 20 mg with AML and HTCZ doses of 5/25 mg, 10/12.5 mg, and 10/25 mg. This covers five of the possible

eight strength combinations and doses not included are those with an OM 20 mg base. Should further positive bioequivalence data be made available, the evaluator believes having five of the possible eight dose combinations would not affect clinical practice as it would be expected those requiring three antihypertensive medications would be on the higher OM dose. Given the known risk of peripheral oedema with the 10 mg dose of AML, it is important that the combinations with the 5 mg dose have been included.

As there are five proposed strengths of the combination, in order to avoid possible confusion between the doses, the tradename should include the strengths of each component.

The triple combination does not include the 2.5 mg AML dose. This dose is used in small, frail and elderly patients as well as those with hepatic insufficiency. The lack of this amlodipine dose has not been described in the draft PI and needs to be included.

The dosage instructions in the draft PI do not adequately explain how to move patients from dual to triple combination. In addition, the titration explanation for the triple therapy combination doses has missed titrating through two of the middle doses. This would need to be altered if an add-on indication was granted. However, as the evaluator is only recommending an indication based on replacement therapy, such changes are not necessary and dosage would need to be amended to include only information relevant to dose for dose substitution.

The draft PI has combined data from the PIs of the three component therapies and the dual combination therapies with little overall attention to the flow of the document or inclusion of repetitive information. This has a resulted in a PI which needs substantial modifications to make it relevant to the triple therapy. The suggested alterations are beyond the scope of the AusPAR.

In summary, the evaluator finds there are positive clinical efficacy data together with safety risks in line with dual therapy which result in a benefit-risk balance in favour of a replacement or substitution indication in the treatment of primary hypertension. However, the bioequivalence and bioavailability testing program described in the dossier is not directly targeted to the Australian market. In particular, comparability of the monotherapy components of AML and HCTZ used in the bioequivalence and bioavailability studies to those available in Australia has not been addressed. If this was satisfactorily addressed then the replacement indication could cover patients who are already adequately controlled on triple therapy (OM, AML and HTCZ) taken as a dual component plus single component formulation at the same dose level. The lack of bioequivalence with three mono-components means this substitution cannot be covered in the replacement indication. In addition, due to the lack of bioequivalence data or request for biowaivers for the middle three proposed doses, this replacement indication should only cover the two doses of 20/5/12.5 mg and 40/10/25 mg.

In line with treatment guidelines and rational and sensible use of therapeutic products, the evaluator does not support the use of a triple therapy for second line use. In addition, due to the lack of clinical studies, the indication for add-on therapy where the patient is inadequately controlled on dual therapy is also not supported. This is in line with recent guidelines from the EMA on the clinical investigations required to support an add-on therapy indication for hypertension treatments.

Finally, the PI needs substantial changes and long term efficacy and safety data needs to be confirmed by the evaluation of the 40 week extension study of the pivotal efficacy trial (CS8635-A-U301).

First round recommendation regarding authorisation

The evaluator does not recommended authorisation of Sevikar HCT in the proposed indication of:

Sevikar HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

However, following satisfactory responses to the questions raised (see *Second round evaluation of clinical data submitted in response to questions*, below) and compliance with requested changes to the PI and CMI[5], then substitution therapy could be recommended. The evaluator also recommends inclusion of the dosage strengths in the product name.

The recommended indication is:

> *Sevikar HCT is indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) with a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.*

Second round evaluation of clinical data submitted in response to questions

The following section provides the TGA evaluation of responses to clinical questions raised by the TGA after the first round evaluation of clinical data including biopharmaceutical aspects. See Attachment 2 (Extract from the CER) for full details, including summaries of the sponsor responses.

[Note that all matters relating to bioavailability and bioequivalence identified below as outstanding issues by the clinical evaluator were satisfactorily addressed prior to the final decision for this application (see also *Overall conclusion and risk/benefit assessment*, below, in this AusPAR).]

Biopharmaceutic aspects

TGA clinical question 1:

Please justify the absence of bioavailability data for the proposed Sevikar HCT 40/5/12.5, 40/10/12.5 and 40/5/25 tablet presentations [addressing the chemistry and clinical requirements set out in section 4 of Appendix 154 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)].

Evaluator's comments:

The bioequivalence study with the highest and lowest dose Sevikar HCT can be extrapolated to the intermediate dose combinations on the proviso that the sponsor provides validation of the experimental methods for the FDC dissolution studies conducted in pH 1.2 phosphate buffer and pH 4.5 phosphate buffer (see question 5 below).

TGA clinical question 2:

Please confirm that the formulations for the Benicar HCT tablets used in the provided biopharmaceutic studies are quantitatively identical to Olmetec Plus formulations registered in Australia. If this is not the case, please provide a justification as to why data establishing bioequivalence between the Benicar HCT tablets used in the provided biostudies and Olmetec Plus or other comparable Australian supplied fixed dose combinations are not required

[5] Details of recommended revisions to product literature are beyond the scope of the AusPAR

(addressing the chemistry and clinical requirements set out in section 4 of Appendix 15 of the ARGPM).

Evaluator's comments:

In regards to the Sevikar/Azor component, since the formulations are identical no further response is required from the sponsors.

In regards to the Antacal component, as the excipients of Norvasc and Antacal are identical, they are both products of the same parent company and as Antacal is bioequivalent to the AML component of Azor no further response is required by the sponsor.

In regards to the HCTZ component, the evaluator accepts that at the highest and lowest doses the HCTZ administered alone (1A Pharma product) and HCTZ administered as Benicar HCT (same as Olmetec Plus in Australia) were bioequivalent, as described in Study E105. However, the "Guideline on the investigation of bioequivalence" (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) states that:

"Comparative in vitro dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation.

Complete documentation of in vitro dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics."

To this end the sponsor has provided the following information regarding the dissolution studies:

- batch number of test and reference batches;
- stated that the method used for dissolution testing was taken from United States Pharmacopoeia (USP);
- respective summary statistics; and
- individual and mean results for 12 replicate experiments.
- Whereas, the sponsor has not provided the following information:
- detailed experimental conditions; and
- validation of experimental methods.

In cases where a USP method has been followed then full validation of the methodology is not required; however, the sponsor must at least demonstrate that in their hands the method is performing as expected, that is, according to USP acceptance criteria. The sponsor has not provided this information.

Evaluator's conclusion

Prior to registration of Sevikar HCT for substitution therapy the sponsor should provide information regarding the exact experimental conditions used in the HCTZ dissolution studies as well as evidence that in the sponsor's hands the method used complies with USP acceptance criteria.

Pharmacokinetics

TGA clinical question 4:

The sponsor is requested to provide any information regarding the similarities between the forms of amlodipine besylate and hydrochlorothiazide used in the bioequivalence/ bioavailability development program and those available on the Australian market, for example bioequivalence studies or dissolution profiles.

Evaluator's comments:

The evaluator is satisfied that the two formulations are identical and no further response is required from the sponsor.

TGA clinical question 5:

The sponsor is requested to provide a formal Justification for a Biowaiver in regards to the bioequivalence and dose proportionality of the three intermediate doses of the Sevikar-HCT MIF, that is, 40/5/12.5 mg OM/AML/HCTZ, 40/5/25 mg OM/AML/HCTZ and 40/10/12.5 mg OM/AML/HCTZ.

Evaluator's comments:

A Biowaiver is appropriate for the intermediate-dose strengths of the FDC tablets on the proviso that the sponsor provides validation of the experimental methods used in the dissolution studies conducted on the FDC tablets in pH 1.2 phosphate buffer and pH 4.5 phosphate buffer. Note: validation has only been provided for dissolution in the pH 6.8 buffer.

TGA clinical question 6:

The sponsor is requested to please justify why studies examining the bioequivalence between the recognised reference formulations of the individual mono-components and the FDC Sevikar HCT MIF have not been undertaken in accordance with EU guidelines CHMP/EWP/240/95 Rev. 1.

Evaluator's comments:

As the sponsor describes the *EU Guideline on Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev. 1) states that in cases where the FDC contains known active substances and it is a substitution indication: *"bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination)."*

In the present application the individual mono-components have not been studied in accordance with the guidelines. Therefore, it is recommended that Sevikar HCT should only be registered as a substitution therapy in patients whose blood pressure is already adequately controlled on the triple combination of OM, AML and HCTZ taken as a dual–component formulation with a single-component formulation, all components at the same dose level on the proviso that the sponsor provides the relevant information regarding the dissolution studies described in the evaluator's responses to question 3 and question 5 above.

TGA clinical question 7:

For study CS8635-A-U301, data from the 40 week open label Period III (weeks 12 to 52) were not provided in the dossier. The first part of the study was completed in 2009 so the data

should be available. As this extension study may provide relevant information on the persistence of efficacy and tolerance, the sponsor is requested to submit the full clinical study report for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these efficacy data.

The sponsor included a copy of the CSR for Study CS8635-A-U301. The sponsor contended that long term efficacy and safety of the three products used in combination had previously been submitted to the TGA in relation to the Sevikar dossier and in the form of the Periodic Safety Update Reports (PSURs) for Olmetec. It was noted that the triple combination was introduced into the PSURs from 25 April 2010 (PSUR #17).

Study CS8635-A-U301 included Period III which was a 40 week open label treatment period (weeks 12 to 52) during which all subjects switched to OM 40 + AML 5 + HCTZ 12.5 mg. After 2 weeks subjects not their achieving BP goal were randomly titrated to OM 40 + AML 10 + HCTZ 12.5 or OM 40 + AML 5 + HCTZ 25 and then if necessary to OM 40 + AML 10 + HCTZ 25. There were 2112 subjects who entered Period III with 15% discontinuing, 6% due to an AE. The Period completion rate was 85%. There were 2098 (99.3%) in the efficacy dataset.

At week 12 the msDBP and msSBP was 82.3 mmHg and 134.8 mmHg, respectively. At the week 52 endpoint, the msDBP ranged from 77.8 to 82.5 mmHg and msSBP ranged from 125.0 to 136.8 mmHg. There was no statistically significant difference in mean change from week 14 to 16 in msDBP or msSBP between the two initial titration regimens. There were 51.3% of subjects at BP goal at week 12 and by week 52 the proportion of subjects who had reached their BP goal ranged from 44.5% to 79.8%. At week 52, the mean reduction in msDBP was -19.4 to -22.1 mmHg and msSBP was -37.2 to -39.1 mmHg.

Efficacy was maintained in subgroups of age, gender, race, ethnicity, diabetes and renal impairment. Subjects with severe or stage 2 hypertension, or BMI ≥30 kg/m^2, at baseline had higher BP at week 52 than those with less severe hypertension or BMI <30 kg/m^2.

Evaluator's comments:

The open label period of Study CS8635-A-U301 demonstrated maintenance of efficacy over 12 months when treatment was titrated to the maximal triple therapy dose. Efficacy was consistent across the subgroups.

TGA clinical question 8:

As stated above, the 40 week open label Period III of study CS8635-A-U301 should also provide relevant long term safety and tolerability data on the triple combination. The sponsor is requested to provide these data, unedited and unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these safety data.

The sponsor included the CSR for Period III of CS8635-A-U301, although again stated that the Sevikar dossier submitted in 2008 included long term data on the triple combination and further data were provided in the PSURs. The sponsor also stated that any additional safety data from Study U301 would have already been included in the Sevikar PI.

The safety population for the open label Period III of CS8635-A-U301 included 2112 subjects of whom 869 subjects received OM 40 + AML 5 + HCTZ 12.5 mg, 246 received OM 40 + AML 5 + HCTZ 25 mg, 239 received OM 40 + AML 10 + HCTZ 12.5 mg and 758 subjects received OM 40 + AML 10 + HCTZ 25 mg as their final dosing regimen. During the 40 week open label period, the mean exposure to the highest dose (40/10/25) was twice that of the lower dose combinations (200.8 days versus 104-117.3 days).

During this period the AE rates was 71.7%, with the highest rate in the highest dose group (59.1%) compared to the other doses (36.4% to 46.8%). The rate of treatment-related AEs

was 25.4%. The rate of mild, moderate and severe AEs was 33.9%, 30.4% and 7.4%, respectively. The rate of SAEs was 5.0% with 6 events (in 5 subjects) deemed treatment-related (2 acute renal failure and 1 each of hyperkalaemia, presyncope, syncope and hypotension). There were 3 deaths which were not considered treatment related (pharyngeal abscess, unknown cause, artery obstruction syndrome). Discontinuations due to AEs occurred in 6.0% of subjects and 3.4% had a treatment-related AE leading to discontinuation.

The most frequent AEs were upper respiratory tract infection (URTI, 28.7%), dizziness (7.8%), nasopharyngitis (6.1%), peripheral oedema (5.7%) urinary tract infection (4.6%) and headache (4.7%). Adverse events of special interest are summarised in Table 3. The most frequent were dizziness and vertigo (9.2%) followed by oedema (6.3%0,glycaemic control (5.2%), headache (4.8%), hepatic related AEs (4.0%), gout, hyperuricaemia and increased uric acid (4.0%) and renal impairment AEs (3.0%).

Table 3. Number (%) of subjects with Adverse Events in Adverse Events Categories of Special Interest– Period III Safety Set

Adverse Event Category [1]	OM40/ AML5/ HCTZ12.5 (N = 2112) n (%)	OM40/ AML5/ HCTZ25 (N = 627) n (%)	OM40/ AML10/ HCTZ12.5 (N = 652) n (%)	OM40/ AML10/ HCTZ25 (N = 790) n (%)	Total (N = 2112) n (%)
Edema	45 (2.1)	12 (1.9)	27 (4.1)	55 (7.0)	133 (6.3)
Hypotension	25 (1.2)	3 (0.5)	8 (1.2)	8 (1.0)	44 (2.1)
Headache	48 (2.3)	16 (2.6)	17 (2.6)	26 (3.3)	101 (4.8)
Dizziness and vertigo	108 (5.1)	24 (3.8)	25 (3.8)	47 (5.9)	194 (9.2)
Syncope	5 (0.2)	1 (0.2)	3 (0.5)	7 (0.9)	16 (0.8)
Renal impairment AEs	30 (1.4)	12 (1.9)	8 (1.2)	14 (1.8)	63 (3.0)
Hepatic-related AEs	51 (2.4)	10 (1.6)	7 (1.1)	18 (2.3)	85 (4.0)
Hyperkalemia	17 (0.8)	4 (0.6)	2 (0.3)	3 (0.4)	26 (1.2)
Hypokalemia	26 (1.2)	3 (0.5)	1 (0.2)	19 (2.4)	48 (2.3)
Glycemic control	67 (3.2)	5 (0.8)	12 (1.8)	31 (3.9)	112 (5.3)
Injury, falls, and fractures	29 (1.4)	3 (0.5)	10 (1.5)	23 (2.9)	64 (3.0)
Gout, hyperuricemia, and increased uric acid	49 (2.3)	9 (1.4)	6 (0.9)	22 (2.8)	84 (4.0)

1. See Section 6.7.1.7.1 for the Medical Dictionary for Regulatory Activities terms included in the various adverse event categories of interest.

AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.3.1.6

The rate of marked chemistry abnormalities was generally greater with OM 40/AML 10/HCTZ 25 mg although exposure duration may have contributed to this.

Evaluator's comments:

The rates of AEs were highest with the highest dose of triple therapy, although the exposure duration to this dose was also greater. Adverse event-related discontinuations over the 40 week period remained relatively low indicating treatment tolerance. Treatment-related SAEs were infrequent (0.2%).The AE profile was consistent with earlier data evaluated and no particular safety signals were evident.

TGA clinical question 9:

Are there any post-marketing data with the triple combination following marketing in the US and elsewhere? If so, this safety information needs to be provided and included in a designated section in the Australian PI. In addition, are there any relevant safety data from the fixed dose combinations of olmesartan/amlodipine or olmesartan/hydrochlorothiazide which need to be included? If so, the sponsor is requested to provide these data, unedited, unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission.

The sponsor stated that the triple combination has been included in the Olmetec PSURs since the 17th report. The most recent PSUR (number 21, 866-021, dated 10 December

2012) was included in the response. The sponsor maintained that all safety information arising from post-marketing data obtained with the triple combination olmesartan medoxomil with hydrochlorothiazide and amlodipine has already been included in the *Adverse Events* section of the PI under subheadings for the individual components.

The Olmesartan medoxomil PSUR 21 reported an estimated patient exposure to OM with AML and HCTZ during this period of 401,850. There were 173 medically confirmed reports with the triple therapy with an adverse drug reaction (ADR) report rate per 10,000 patients of 4.3. With the triple therapy there were 20 serious cases and one death reported of lactic acidosis and acute renal failure. The most frequent events were oedema peripheral, nausea, dizziness, drug ineffective, oedema and pain in extremity.

The company core datasheets for OM + AML and OM + AML + HCTZ were updated to include the interaction between amlodipine and simvastatin as follows: *'Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.'*

Following findings of increased cardiovascular deaths in two studies of olmesartan in diabetic patients (ROADMAP and ORIENT), additional analyses regarding cardiovascular risks were performed. This meta-analysis and an epidemiological study were completed and the sponsor reported that they did not show an increased cardiovascular risk with OM compared to the control group nor raise any concerns regarding the safety of OM compared to other angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors. The results were submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in the EU. This committee requested that the main findings from the ROADMAP and ORIENT studies be included in the product information of all olmesartan-containing products in the EU. In addition, the EU Risk Management Plan (RMP) for the triple combination was updated to include cardiovascular risk in diabetic patients.

Evaluator's comments:

The information relating to the interaction between amlodipine and simvastatin is not currently in the draft Sevikar HCT PI and should be included. The information relating to cardiovascular risk should be considered for inclusion in the PI.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of OM/AML/HCTZ in the proposed usage are largely unchanged from those identified in the *First round assessment of benefits*, above, apart from the following two points:

- A maintenance of efficacy over 12 months of treatment with no additional safety signals.
- The MIF was bioequivalent with the combination of Benicar HCT (OM/HCTZ) and Antacal (AML) and the combination of Azor (OM/AML) and HCTZ for both the highest (40/10/25 mg) and lowest (20/5/12.5 mg) doses. In addition, based on data provided in the biowaiver, the middle three dose strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg) are also considered equivalent to the clinical formulations.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of OM/AML/HCTZ in the proposed usage are unchanged from those identified in the *First round assessment of risks* with the exception of the following points.

- As it has been confirmed that the amlodipine used in the bioequivalence and bioavailability program is equivalent to that available on the Australian market, this risk is no longer applicable. In relation to equivalence of HCTZ available in Australia, further information is required on the dissolution testing.[6]
- The risk regarding lack of bioequivalence of the three intermediate dose strengths is no longer valid as the data presented in the biowaiver was acceptable (subject to data on dissolution study methodology).

Second round assessment of benefit-risk balance

After evaluation of the sponsor's responses to questions, the evaluators make the following points.

The pivotal Study CS8635-A-U301 had a 40 week open label Period III (weeks 12 to 52) and the data from this indicated that efficacy is maintained and no additional safety signals were evident over this period.

The sponsor provided data which established the equivalence for amlodipine used in the clinical program with those on the Australian market. By contrast, the sponsor has failed to provide the necessary dissolution data (experimental conditions and validation of methods) that would allow the evaluator to assume the formulations of HCTZ used in the clinical trials are equivalent to that available in Australia. Prior to registration, the sponsor should provide information regarding the exact experimental conditions used in the HCTZ dissolution studies as well as evidence that in the sponsor's hands the method used complies with USP acceptance criteria.

As noted in the first round evaluation, bioequivalence was found for the highest and lowest dose strength but no biowaiver was requested for the three other dose strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg). This has now been provided and included data showing similar and dose proportional tablet composition, comparable dissolution profiles, a lack of drug-drug interaction between the components of the triple therapy and dose proportional PK. The experimental methods used in the dissolution studies conducted on the FDC tablets were not provided. Assuming this is provided and is satisfactory, then, given the findings listed above, the evaluator believes a biowaiver is appropriate.

On the assumption that the two issues above relating to dissolution testing have been addressed, then the bioequivalence data allow substitution of the dual plus single component therapy (OM/AML plus HCTZ or OM/HCTZ plus AML) with the triple combination.

It still remains that bioequivalence between the MIF triple combination and the three mono-components has not been established[7] and so an indication which supports direct substitution between single components and the triple combination is not supported.

The evaluator's recommendation regarding the indication remains as outlined after the first round evaluation. That is, the triple combination should only be used as third line

[6] This matter was satisfactorily addressed prior to the final decision for this application (see also *Overall conclusion and risk/benefit assessment*, below, in this AusPAR).
[7] All matters relating to bioavailability and bioequivalence were satisfactorily addressed prior to the final decision for this application (see also *Overall conclusion and risk/benefit assessment*, below, in this AusPAR).

therapy as direct substitution for patients already controlled on a dual component and single component formulation. There are insufficient clinical data to support an add-on therapy indication.

It is still recommended that as there are five proposed dose strengths of the combination, in order to avoid possible confusion between the doses, the tradename should include the strengths of each component.

The draft PI needs substantial modification[8]. The sponsor needs to ensure that the PI only includes information that is relevant to direct dose-for-dose substitution from dual plus single therapy to triple therapy.

It is also recommended that the sponsor provide information to the TGA relating to recent discussions with the European Authorities on cardiovascular risk which resulted in recommendations to include further data in the product information of olmesartan-containing medicines. This should include a discussion on whether additional data should also be required in the relevant Australian PI documents.

In summary, the evaluator finds there are positive clinical efficacy data together with safety risks in line with dual therapy which result in a benefit-risk balance in favour of a replacement or substitution indication in the treatment of primary hypertension. This replacement indication must only cover patients who are already adequately controlled on triple therapy (OM, AML and HCTZ) taken as a dual component plus single component formulation at the same dose level.

Second round recommendation regarding authorisation

The evaluator does not recommended authorisation of Sevikar HCT in the proposed indication of:

SEVIKAR HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

If the sponsor satisfactorily addresses the questions relating to the dissolution testing for HCTZ and the fixed dose combination and complies with the requested changes to the PI/CMI then an indication covering substitution therapy is recommended.

The recommended indication is:

> *Sevikar HCT is only indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) with a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.*

The evaluator recommends inclusion of the dosage strengths in the product name. In addition, details of data relating to cardiovascular risks with the olmesartan-containing products that were submitted to the EMA, and the resultant recommended changes to the PI, need to be provided for evaluation.

Comments on clinical aspects of the risk management plan

The sponsor provided new clinical information after the first round evaluation. There was no proposed change to the EU RMP for olmesartan. The evaluator has noted that the PSUR

[8] Details of comments on product literature are beyond the scope of the AusPAR.

(PSUR 21) submitted for the second round of evaluation stated that the [EU] RMP was updated to include cardiovascular risk.

V. Pharmacovigilance findings

During pre-submission assessments the TGA Office of Product Review (OPR) granted the sponsor a waiver from the need to submit a RMP for this application.

VI. Overall conclusion and risk/benefit assessment

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

Background

Olmesartan medoxomil is an orally active angiotensin II receptor (type AT_1) antagonist. It has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor. It is expected to block all actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the AT_1 receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Olmesartan medoxomil is a pro-drug. 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 (GIT).

Currently on the register there are 3 strengths of olmesartan (Olmetec) as a monotherapy: 10 mg, 20 mg and 40 mg. The approved indications are *"Olmetec is indicated for the treatment of hypertension"*.

Currently also on the register are four dosage strengths of the dual fixed-dose combination of OM/HCTZ (Olmetec Plus): 20/12.5, 20/25, 40/12.5 and 40/25 mg, with approved indications *"Treatment of hypertension. Treatment should not be initiated with this fixed dose combination"*.

The dosage instructions for Olmetec Plus are as follows:

> Olmetec Plus is administered once daily, with or without food, in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or HCTZ alone.
>
> Olmetec Plus is registered in combinations of 20/12.5 mg, 20/25 mg, 40/12.5 mg and 40/25 mg.
>
> Dosing should be individualised and dependent on the patient's condition. Depending on the blood pressure response, the dose may be titrated after 4 weeks.
>
> If blood pressure is not adequately controlled on Olmetec alone, HCTZ may be added with a starting dose of 12.5 mg. Should blood pressure still remain inadequately controlled either up-titration of HCTZ to 25 mg or Olmetec to 40 mg dose may be advisable.
>
> If blood pressure is not adequately controlled on HCTZ alone, olmesartan may be added with a starting dose of 20 mg with up-titration to 40 mg should blood pressure still remain inadequately controlled. Doses of Olmetec Plus above 40/25 mg are not recommended.

Currently also on the register are four dosage strengths of the dual fixed-dose combination of OM + AML (Sevikar): 20/5, 20/10, 40/5 and 40/10 mg. The approved indication reads: *"Sevikar is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination (see Dosage and Administration)".*

The dosage instructions for Sevikar are as follows:

> 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.

While there are approved dosage instructions pertaining to children for the monotherapy Olmetec, there are no such instructions for Olmetec Plus or for Sevikar. In the PI for Olmetec Plus there is the statement, *"The safety and efficiency of Olmetec Plus in children have not been established"* and in the PI for Sevikar there is the statement, *"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".* A similar statement is proposed for the Sevikar HCT PI, namely, *"Sevikar HCT is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy".*

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. It 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.

Currently on the register there are numerous versions of amlodipine as monotherapy in strengths of 2.5 mg, 5 mg and 10 mg. The approved indications for amlodipine monotherapy are two-fold:

"Hypertension – Norvasc is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of Norvasc, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent or an angiotensin-converting enzyme inhibitor.

Angina – Norvasc is indicated for the first line treatment of chronic stable angina. Norvasc may be used alone, as monotherapy or in combination with other antianginal drugs"

Amlodipine is also currently on the register in a number of fixed-dose combinations, both dual and triple. Examples of dual combinations are amlodipine (5 or 10 mg) in combination with atorvastatin, perindopril arginine, valsartan, telmisartan olmesartan (as above) and aliskiren. Examples of triple combinations are amlodipine (5 or 10 mg) with valsartan + HCTZ and with aliskiren + HCTZ.

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

There is currently on the register one strength of Dithiazide (HCTZ on its own), 25 mg which is approved for, *"Hypertension: May be used alone or in combination with other antihypertensive drugs. Oedema: Associated with congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, premenstrual tension and drug induced Oedema"*. For hypertension, the usual starting dose is 25 or 50 mg a day as a single or divided dose and the dosage should be adjusted according to blood pressure response. The maximum recommended daily dose is 100 mg. In the approved PI there is a further note that when thiazides are used with other antihypertensives, the dose of the latter may need to be reduced to avoid excessive decrease in blood pressure.

Currently registered triple fixed-dose combinations: It should be noted that there are only two triple fixed-dose combination products presently registered in Australia for the treatment of hypertension, namely valsartan + amlodipine + HCTZ (160/5/12.5, 160/5/25, 160/10/12.5, 160/10/25 and 320/10/25 mg) and Aliskiren + Amlodipine + Hydrochlorothiazide (150/5/12.5, 300/5/12.5, 300/5/25 and 300/10/25 mg). These currently registered triple fixed-dose combinations are only approved for substitution or replacement therapy, that is, where someone is already on the triple combination taken either as three separate monotherapies or as a dual-component formulation with a single-component formulation, with all components at the intended dosage strengths.

Overseas regulatory status

USA: The FDC was approved 23 July 2010 for the indication "*Tribenzor[9] is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. Tribenzor is not indicated for initial therapy*".

EU: The FDC was first approved 21 December 2010 for treatment of essential hypertension but as substitution therapy only. The next approved was in 2012 for "*Treatment of essential hypertension.* ***Add-on therapy*** *Sevikar HCT is indicated in adult patients whose blood pressure is not adequately controlled on the combination of olmesartan medoxomil and amlodipine taken as dual-component formulation.* ***Substitution therapy*** *Sevikar HCT is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component (olmesartan medoxomil and amlodipine or olmesartan medoxomil and hydrochlorothiazide) and a single-component formulation (hydrochlorothiazide or amlodipine)*". The latter indication is approved in 20 or so EU member states including France, Germany and UK.

Switzerland: The FDC was approved 20 May 2011 for the substitution indication "*Treatment of essential hypertension. SEVIKAR HCT is indicated as substitution therapy in*

[9] Tribenzor is the trade name of the triple fixed-dose combination of olmesartan medoxomil + amlodipine + hydrochlorothiazide in the USA.

adult patients whose blood pressure is adequately controlled by a combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken either in the form of three single-component formulations or in the form of a dual-component formulation plus a single-component formulation". The FDC is currently being evaluated for the indication: "*Treatment of essential hypertension. SEVIKAR HCT is indicated in patients whose blood pressure is not adequately controlled by a dual-component therapy. SEVIKAR HCT is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled by a combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken either in the form of three single-component formulations or in the form of a dual-component formulation plus a single-component formulation*" (application submitted 26 September 2012).

Delegate's comments: The Delegate notes that in both the EU and Switzerland, the applications were each made in 2 steps, the first being for substitution therapy only and the second being for an extension of that indication to include an add-on therapy indication. The Delegate requested the sponsor, in the response to the Overview, to clarify precisely what data was submitted to each of the relevant regulatory authorities for each of these two steps and how these data compare with the data provided to the TGA for this submission. In particular, the Delegate wished to know whether there were any extra data, documents, reviews or analyses provided to either regulatory authority for the second step, the extension of indication, that is, subsequent to the submission which resulted in approval of a substitution indication only. Were any of these extra data, documents, reviews or analyses specifically requested by the relevant regulatory authority? If so, the sponsor was asked to provide full details of the requests made and how they were answered. In each case, the sponsor was requested to give details of the indication which was actually sought by the marketing authorisation holder or sponsor at the time of the first application (or first step).

Guidelines

There are a number of TGA-adopted European guidelines relevant to this submission, besides the general guidelines:

CPMP/EWP/238/95 Rev 2 (pdf,100kb)
Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension
Effective: 15 June 2006

CPMP/EWP/240/95 Rev. 1 (pdf,81kb)
Guideline on Clinical Development of Fixed Combination Medicinal Products
Effective: 28 May 2010

pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)
Clinical Investigation of Medicinal Products for Long-Term Use
Effective: 12 February 2002
See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

EMEA/CHMP/EWP/311890/2007 (pdf,105kb)

Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention
Effective: 29 June 2009

EMA/CHMP/EWP/191583/2005 (pdf,34kb)
Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention
Effective: 17 December 2010

See also: CPMP/EWP/240/95 Rev. 1 Guideline on Clinical Development of Fixed Combination Medicinal Product

CHMP/EWP/185990/06 (pdf,64kb)
Guideline on Reporting the results of Population Pharmacokinetic Analysis
Effective: 27 January 2009

CPMP/QWP/EWP/1401/98 Rev 1 (pdf,237kb)
Guideline on the Investigation of Bioequivalence
Effective: 16 June 2011
Adopted by TGA with the following notation:

"While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.

The procedure for abridged applications claiming essential similarity to a reference product (that is, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia."

EMEA/CHMP/EWP/297931/2008 (pdf,32kb)
Concept Paper/Recommendation on the Need for Revision of (CHMP) Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
Published TGA Internet site for information only, effective: 10 February 2009

CPMP/EWP/560/95 (pdf,79kb)
Note for Guidance on the Investigation of Drug Interactions
Effective: 19 April 2001

Quality

There were a number of chemistry and quality issues raised following the initial evaluation of this application but all issues were satisfactorily resolved. The quality evaluator has no objections to the registration of this product with respect to chemistry, manufacturing and controls. The three active pharmaceutical ingredients are manufactured and controlled in the same manner as the corresponding substances used in finished products currently registered to the sponsor. The stability data provided supports a shelf life of 36 months when stored below 25°C in the proposed packaging.

Nonclinical

The nonclinical data provided by the sponsor in support of the safety of Sevikar HCT tablets consisted of an initial 28-day dose-range finding study in rats followed by a GLP-standard 3-month rat toxicity study (with accompanying toxicokinetics) which evaluated the potential for any new toxicities caused by concurrent oral administration of the triple combination of OM, AML and HCTZ. It was judged to be an appropriate data package for a fixed combination of previously approved components.

Toxicokinetic data from the 28-day and the 3-month studies in rats showed that OM + HCTZ treatment had no effect on the systemic exposure to AML (based on AUC) but co-administration of AML dose-dependently increased systemic exposure (AUC) to both OM and HCTZ. This finding was previously noted with the OM + AML combination (Sevikar) and was shown to result from an AML-induced decrease in intestinal motility at high AML

exposures that leads to markedly higher plasma levels of olmesartan in rats. However, no evidence for such an interaction was seen in the human PK data with the combination.

No novel toxicities were observed in the pivotal rat 13-week, repeat dose oral study which was well conducted and GLP-compliant. Most of the changes reflected the known pharmacological actions of AML or OM. Animals dosed with the triple combination of OM, AML and HTCZ showed a similar toxicological profile to those dosed with the dual combination of OM and HCTZ despite the marked increase in plasma olmesartan levels.

The nonclinical evaluator was of the opinion that the toxicities observed have been described previously for these drugs or for drugs of the same class and reflect organ toxicities that are able to be monitored clinically. As all three mono-therapies have been approved and on the market for some years and as there are extensive nonclinical and clinical data available (for both the compounds alone and as various dual combinations), the nonclinical evaluator was of the opinion that there were no novel clinical safety concerns signalled by the nonclinical data.

There were no nonclinical objections to the registration of Sevikar HCT tablets for the treatment of hypertension. The non-clinical evaluator recommended a number of amendments to the PI[10] and the Delegate supports these amendments.

Clinical

Pharmacokinetics

There were 5 single dose bioequivalence studies in healthy adults and the most important of these was CS8635-A-E105. The latter study compared the PK of the MIF to two reference clinical formulations, Benicar HCT + Antacal and Azor + HCT. Benicar is not the same as Sevikar. Benicar is the US-approved formulation of olmesartan, Benicar + HCTZ is the US-approved formulation of OM + HCTZ while Sevikar is the Australian-approved formulation of OM + AML. Antacal is an overseas amlodipine product. Azor is the US-approved formulation of OM + AML. Thus Benicar HCT + Antacal [OM/HCTZ + amlodipine] and Azor + HCTZ [OM/AML + HCTZ] each represent the triple combination of OM/AML/HCTZ. In answer to a TGA request for further information the sponsor was able to confirm that Benicar HCT [US-registered] is identical to Olmetec Plus [Australian-registered] and that Azor [US-registered] is identical to Sevikar [Australian-registered]. Antacal (AML) is a product of a subsidiary of Pfizer. The excipients contained in Antacal (Europe) and Norvasc (Australia) are identical. Bioequivalence was demonstrated between the HCTZ monotherapy formulations and the HCTZ component of Benicar HCT (and thus Olmetec Plus).

Of the remaining 4 single dose bioequivalence studies in healthy adults, there were two, CS8635-A-U101 and-U102, which also tested for any PK interactions between any of the 3 active components while the other two, CS8635-A-U103 and-U104, involved pilot formulations of the triple FDC. There was one single dose food effect study, CS8635-A-U106, of the MIF at the highest dosage strength, 40/10/25 mg, under both fasting and fed conditions.

The population PK analysis used data from 3 clinical development programs: CS866 (OM + HCTZ), CS-8663 (OM + AML) and CS-8635 (OM + AM + HCTZ). The dataset contained a total of 13 Phase I clinical pharmacology studies [3 from the CS866 program, 4 from the CS8663 program and 6 from the CS-8635 program]. It also contained data from 2 Phase III studies, CS8663-A-U301 and CS8635-A-U301.

[10] Details of these are beyond the scope of the AusPAR.

No studies examined the bioequivalence of the MIF of Sevikar HCT and individual doses of the 3 active components. However in response to a TGA request for information, a comprehensive and acceptable justification for a biowaiver with regards to bioequivalence and dose proportionality of the three intermediate doses was provided by the sponsor. Based on similar tablet composition, equivalent dissolution profiles, lack of drug-drug interaction of Sevikar HCT components, bioequivalence of the lowest and the highest MIFs and the dose-proportional composition of the 5 MIFs, all of the market formulations were considered to be bioequivalent to their corresponding component formulations.

The MIF and two reference but overseas composite products [Benicar HCT + Antacal and Azor + HCTZ, each a composite of a different dual combination and a monotherapy but each containing the same 3 active ingredients] were bioequivalent at 2 dose strengths, OM/AML/HCTZ 40/10/25 mg and 20/5/12.5 mg (note the comments above about Benicar HCT, Antacal and Azor).

The 3 active components of the low dose MIF (OM/AML/HCTZ 20/5/12.5 mg) and of the high dose MIF (OM/AML/HCTZ 40/10/25 mg) were bioequivalent when dose normalised, indicating dose proportional PK for the two MIF dosage strengths. Given the information supplied about the identity of various overseas products and the acceptable justifications submitted, dose proportional PK can be assumed across the five proposed dosage strengths.

The PK of the 3 active components of Sevikar HCT following a single dose were bioequivalent with regard to OM and AML AUC and C_{max} in both fasted and fed subjects. By contrast and as noted by the clinical evaluator, although the AUC of HCTZ was bioequivalent between the two groups, the C_{max} of HCTZ was not bioequivalent and was approximately 23% lower in fed subjects. The Delegate agreed with the clinical evaluator that, given that bioequivalence was demonstrated for AUC, the principal parameter of interest with regard to clinical efficacy, the effect of food on C_{max} is not one of major clinical impact. Administration with food decreased the T_{max} of OM and of HCTZ by 1 and 0.5 h, respectively.

Modelling of the data indicated that all 3 compounds were best described by a 2-compartment model consisting of central and peripheral compartments. Olmesartan PK were adequately characterised by a 2-compartment model with first order absorption and time lag. Creatinine clearance was a significant predictor of the apparent oral clearance of olmesartan. Amlodipine PK were adequately characterised by a 2-compartment model with first order absorption and a time lag. Age was a significant predictor of the apparent oral clearance of AML. Hydrochlorothiazide PK were also adequately characterised by a 2-compartment model with first order absorption and a time lag. Sex, age and creatinine clearance were all significant predictors of the apparent oral clearance of HCTZ.

Pharmacodynamics

No studies directly examined the relationship between drug concentration and PD effect. However, the population PK study indicated that the drug effects of OM and AML exposure on trough sDBP and sSBP could be described by an E_{max} model, whereas the drug effect of HCTZ exposure was described by a linear model. In addition, the BP lowering effects of OM, AML and HCTZ in monotherapy, dual combination therapy, and triple combination therapy were well characterised by a model composed of the sum of the individual effects and interaction among the components.

The exposure-response model generated indicated that the baseline trough sDBP and sSBP were significant covariates, with more BP lowering effect associated with higher baseline BP. As might be expected, the simulation results also indicated that BP lowering effects of CS-8635 triple combination therapies were superior to their respective mono and dual treatment of the OM, AML and HCTZ, and the predicted systolic and diastolic BP

lowering effects were in the following order: 20/5/12.5 mg < 40/5/12.5 mg < 40/10/12.5 mg ≈ 40/5/25 mg < 40/10/25 mg for OM/AML/HCTZ, respectively.

Efficacy

Pivotal study

Study CS8635-A-U301 was a Phase III, multicentre, randomised, parallel group study. There were three periods: Period 1 was a washout (3 weeks maximum duration) to determine eligibility; Period 2 was a 12 week double-blind treatment period; and Period 3 was a 40 week open label treatment period and a 2 week follow up. The study was conducted between May 2008 and February 2009 at 317 centres in the US in adults aged at least 18 years with hypertension (after medication washout) defined as a mean seated BP (msBP) ≥ 140/100 mm Hg or a msBP ≥ 160/90 mm Hg with a difference in msSBP and msDBP between 2 consecutive visits before randomisation of ≤ 20/10 mm Hg.

The primary objective was to determine if the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg had a clinically significant benefit versus the respective dual therapy components in controlling blood pressure after 12 weeks of treatment.

After washing out antihypertensive medications, subjects with confirmed eligible BP were randomised in Period II of the study to one of 4 treatment groups: OM 40 mg + AML 10 mg + HCTZ 0 mg (placebo), OM 40 mg + HCTZ 25 mg +AML 0 mg (placebo), AML 10 mg + HCTZ 25 mg + OM 0 mg (placebo), or OM 40 mg + AML 10 mg + HCTZ 25 mg. This randomisation included a treatment sequence to arrive at the final dose. The sequence included either a dual combination or placebo for the first 2 weeks. After 2 weeks the placebo subjects then received dual therapy for 2 weeks. This resulted in all subjects receiving dual therapy between weeks 2 and 4. From week 4 to week 12 treatment reflected the four randomised groups. The Period II treatment assignment is shown in Table 4.

Table 4. Study CS8635-A-U301. Period II treatment assignment

		n	Day 1 to Week 2	Week 2 to Week 4	Week 4 to Week 12
600 subjects		591	OM/AML/HCTZ 40/10/0 mg		OM/AML/HCTZ 40/10/0 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	
	naïve	3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/10/0 mg		
600 subjects		591	OM/AML/HCTZ 40/0/25 mg		OM/AML/HCTZ 40/0/25 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	
	naïve	3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/0/25 mg		
600 subjects		591	OM/AML/HCTZ 0/10/25 mg		OM/AML/HCTZ 0/10/25 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	
	naïve	3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 0/10/25 mg		

*In total, the OM 40 mg + AML 10 mg + HCTZ 25 mg treatment group was comprised of approximately 600 subjects, consisting of 200 subjects from each of the three dual combination assignments at Week 4.
AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

In the 40 week Period III, all subjects were switched to open label OM 40 mg + AML 5 mg + HCTZ 12.5 mg. Those not achieving target BP (<140/90 mmHg or <130/80 mmHg for those with diabetes, chronic renal disease or chronic cardiovascular disease) after 2 weeks were randomly titrated (using an Interactive voice response system (IVRS)) to OM 40 mg + AML 10 mg + HCTZ 12.5 mg or OM 40 mg + AML 5 mg + HCTZ 25 mg. A further titration to OM 40 mg + AML 10 mg + HCTZ 25 mg was allowed at investigator discretion. Once target BP was reached, subjects remained on this dose. Down titration of triple therapy was allowed for hypotension or intolerance, however dual therapy was not allowed.

The primary efficacy outcome was the change from baseline in msDBP at week 12 with last observation carried forward (LOCF). The primary analysis was on the full analysis set (FAS) with LOCF. The FAS included all randomised subjects who received at least one dose of study medication and had a baseline and at least one post baseline msDBP assessment. The per protocol (PP) set included all subjects in the FAS who completed Period II or withdrew before completing Period II due to insufficient treatment effect, and had no major protocol violations. Sample size calculations were acceptable.

The secondary efficacy outcomes were:

- Change from baseline in msSBP at Week 12 with LOCF;
- Change from baseline in msDBP and msSBP at Weeks 6, 8, 10, and 12;
- Change in msDBP and msSBP from baseline at Week 2 (to compare the placebo and each dual combination treatment);
- Proportion of subjects who reached blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease);
- Proportion of subjects who reached blood pressure targets at Weeks 6, 8, 10, 12, and Week 12 with LOCF (that is, <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, msDBP <90 mmHg, and msSBP <140 mmHg); and
- Change from baseline in 24 h ABPM at 12 weeks. This included the change from baseline in mean daytime (8 am to 4 pm), mean night time (10 pm to 6 am) and mean 24 h ABPM; change from baseline in mean ABPM during the last 2, 4, and 6 h of the dosing interval; and the percentage of subjects achieving mean 24 h, daytime, night-time, and last 2, 4 and 6 h ABPM blood pressure targets.

There were a number of other efficacy outcomes, for example, tertiary or exploratory outcomes.

Disposition: There were 6724 subjects enrolled and 2492 randomised to double-blind treatment. The FAS included 2458 (98.6%) subjects and the PP population 2025 (81.3%). There were 628 in the OM 40/AML 10 mg, 637 in the OM 40/HCTZ 25 mg, 600 in the AML 10/HCTZ 25 mg and 627 subjects in the OM 40/AML 10/HCTZ 25 mg group.

The overall discontinuation rate was 15.1% with the highest rate in the triple combination group (17.7%) and a range of 11.3% to 16.6% in the dual combination groups. Adverse events were the most frequent reason for discontinuation (6.2%) with similar rates in the OM 40/AML 10/HCTZ 25 (7.7%), OM 40/HCTZ 25 (7.2%) and AML 10/HCTZ 25 groups (6.3%) and slightly lower in the OM 40/AML 10 group (3.5%). Other reasons for discontinuation were consent withdrawal (3.3%) and loss to follow up (3.2%). Excluding the first four weeks of the study, the discontinuation rate was higher with triple than dual triple combination (10.3% versus 6.4-8.6%) and the main reason was an adverse event (4.0% versus 1.2-2.2%).

Demographic and baseline characteristics were on the whole balanced between groups and no significant differences were found. There were slightly more males (52.9%), two thirds of subjects were Caucasian (66.8%) and approximately 30% Black. The mean age was 55.1 years and the mean BMI 33.1 kg/m^2. The mean duration of hypertension was 9.9 years and 33.5% were treatment naïve.

Primary efficacy outcome: The mean change from baseline to week 12 (with LOCF) in the msDBP was -21.5 mmHg for the triple combination and -17.8 mmHg, -16.5 mmHg and -14.8 mmHg for the OM40/AML 10, OM40/HCTZ 25 and AML 10/HCTZ 25 mg groups, respectively. The reduction in msDBP was statistically significant in all groups ($p<0.0001$). The reduction in msDBP was greater with OM 40/AML 10/HCTZ 25 mg and the least

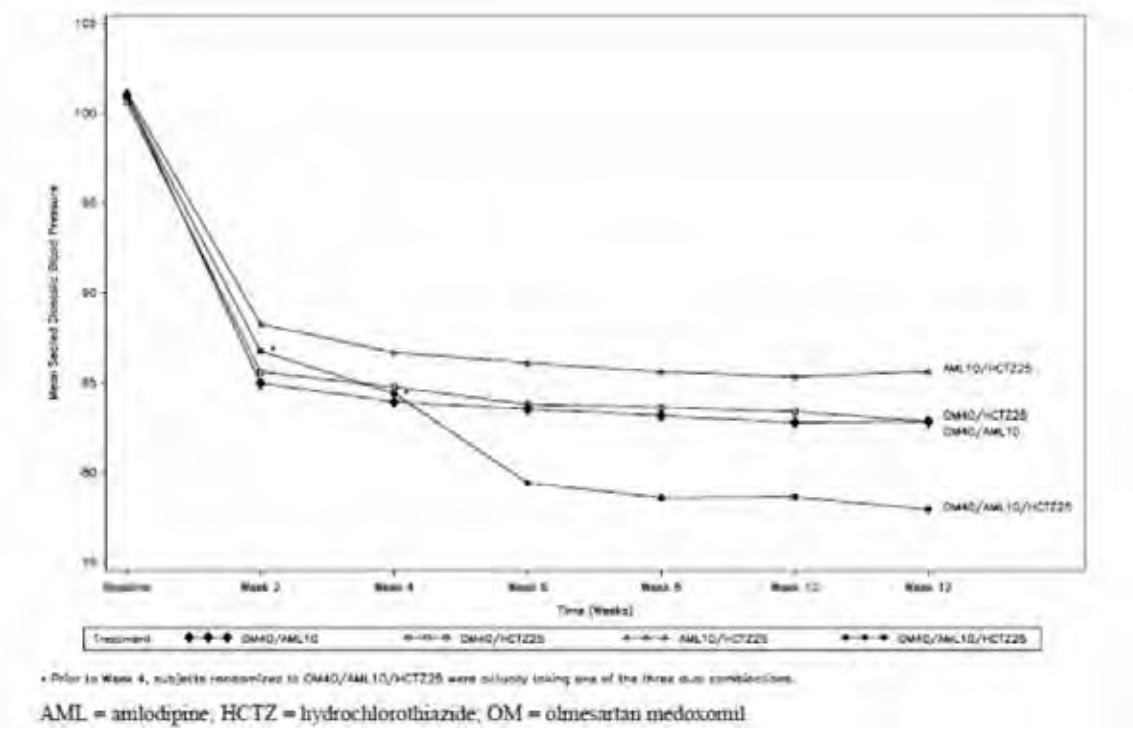
squares (LS) mean difference between the triple therapy and the three dual therapy groups ranged from -3.8 to -6.7 mmHg (p<0.0001).

Secondary and other efficacy outcomes: These were generally consistent with the primary efficacy outcome. In particular, at week 12 with LOCF, the LS mean reduction in msSBP was 37.1 mm Hg for the triple therapy and 27.5 to 30.0 mm Hg for the dual therapy groups with all reductions being statistically significant (p < 0.0001). The LS mean difference between triple and dual therapies in msSBP was also significant (p < 0.0001) and ranged from -7.1 to -9.6 mm Hg and the proportion of subjects reaching their BP target at week 12 (LOCF) was 64.3% with triple therapy compared to 34.9% to 46.6% in the dual therapy groups, again a statistically significant result (p < 0.0001). Results were consistent across subgroups of age, gender, race and hypertension severity. There were too few subjects aged over 75 years or with renal impairment to allow meaningful comparisons.

As part of the TGA request for further information the clinical evaluator requested data from the 40-week open label period or Period III (weeks 12 to 52). The clinical evaluator was able to confirm that this open label period demonstrated maintenance of efficacy over 12 months when treatment was titrated to the maximal triple therapy dose. Efficacy was consistent across the sub-groups.

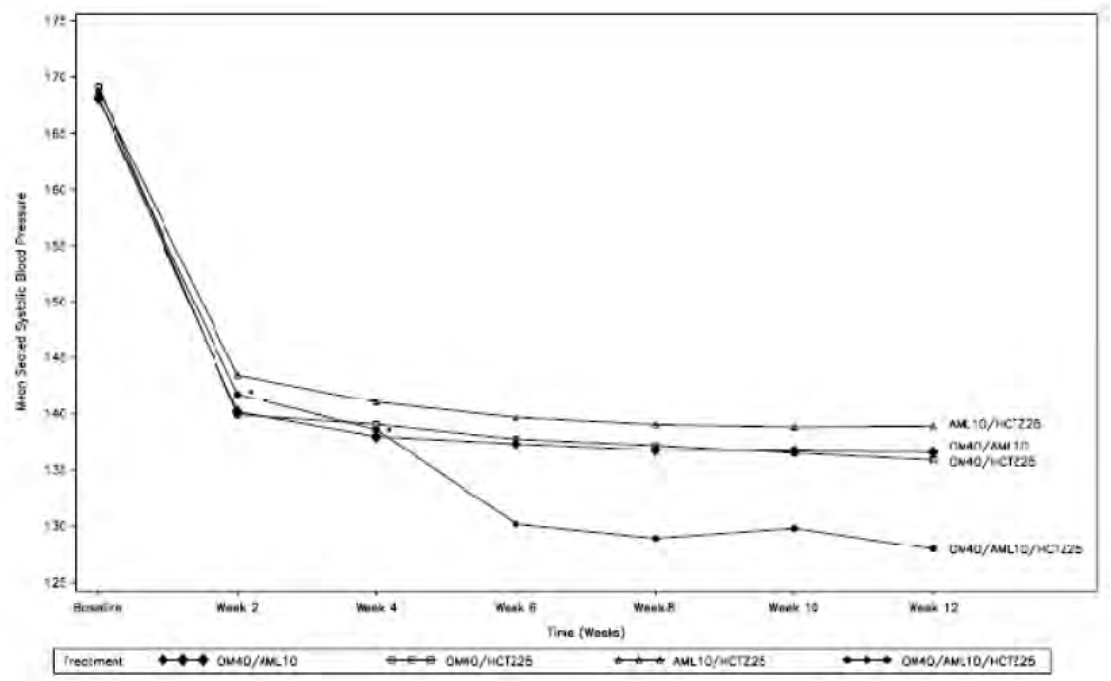
Delegate's comments: The Delegate was somewhat concerned that there appear to be no formal add-on comparisons available from the data-set, that is, that there are no formal comparisons of the results between week 4 and those at week 12. It was after week 4 that one quarter of those on each dual therapy were switched to triple therapy. Out of each group of 800 subjects on dual therapy, 200 were switched to triple therapy while 600 continued on the dual therapy. Some idea of the extent of the improvement is provided in Figure 4, Figure 5 and Figure 6.

Figure 4. Mean seated diastolic blood pressure (mmHG) over time by randomised treatment group – Full analysis set



AML = amlodipine, HCTZ = hydrochlorothiazide, OM = olmesartan medoxomil

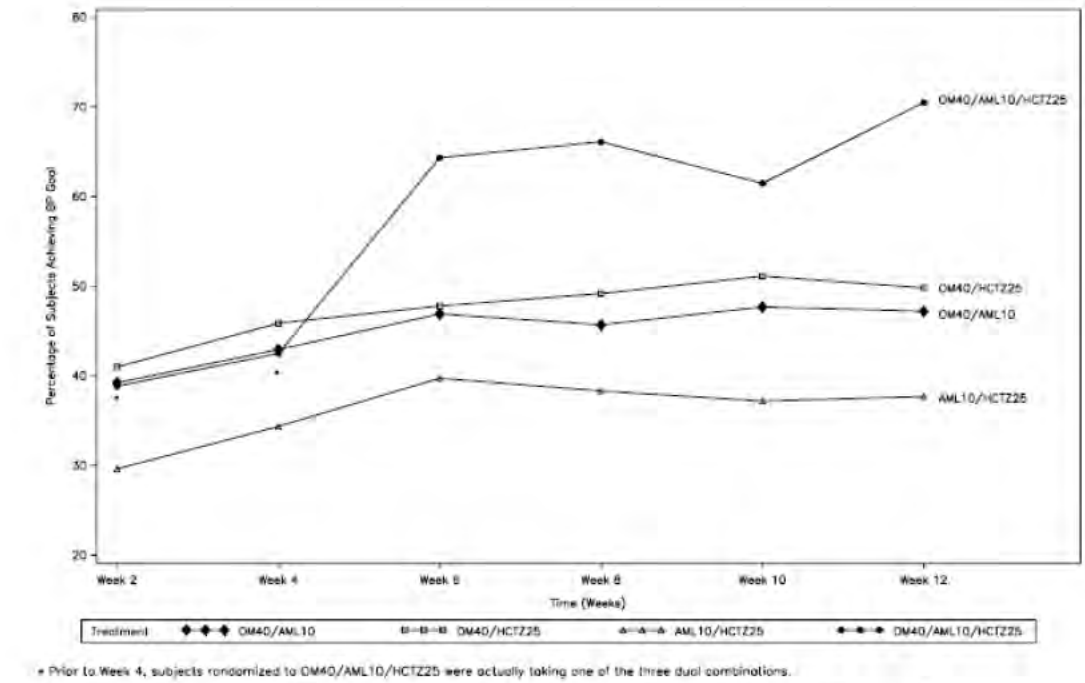
Figure 5. Mean seated systolic blood pressure (mmHG) over time by randomised treatment group – Full analysis set



• Prior to Week 4, subjects randomized to OM40/AML10/HCTZ25 were actually taking one of the three dual combinations.

AML – amlodipine; HCTZ – hydrochlorothiazide; OM – olmesartan medoxomil.

Figure 6. Percentage of subjects achieving blood pressure foal over time by randomised treatment group – Full analysis set



• Prior to Week 4, subjects randomized to OM40/AML10/HCTZ25 were actually taking one of the three dual combinations.

AML = amlodipine; BP = blood pressure; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Respectively, these figures show the msDBP, msSBP and the percentage of subjects achieving BP goal, all parameters being shown over time from baseline to week 12. In each case the improvements from weeks 4 to 8 are visible. However, as mentioned add-on effects in those subjects actually exposed to the add-on therapy have not been formally assessed.

In the response to this Overview, the sponsor was requested to comment on this deficiency and, if the sponsor wished, to present appropriate post hoc analyses which support the add-on claim. For example in order to assess a claim for a true add-on effect, there would have to be studies of 3 particular sub-groups in this pivotal study. There were 200 subjects who, in the last 8 weeks of the study, were on OLM/AML/HCTZ 40/10/25 after having had HCTZ 25 mg added to their previous therapy of OLM/AML/HCTZ 40/10/0 (effectively dual therapy). All of the comparisons of msDBP, msSBP and proportion of patients achieving target need to be performed for this group of patients. Similarly, there were 200 subjects who, in the last 8 weeks of the study, were on OLM/AML/HCTZ 40/10/25 after having had AML 10 mg added to their previous therapy of OLM/AML/HCTZ 40/0/25 (effectively dual therapy) and there were 200 subjects who, in the last 8 weeks of the study, were on OLM/AML/HCTZ 40/10/25 after having had OLM 40 mg added to their previous therapy of OLM/AML/HCTZ 0/10/25 (effectively dual therapy). Again, the requested comparisons need to be made for these two groups. All comparisons will need to be between the results at the end week 4 and the results at the end week 12. Essentially, the pivotal study is a parallel-group study with no formal or convincing evaluation of add-on effect. It would seem that the sponsor may have already done these analyses as the between-treatment comparisons summarised in the proposed PI are not the same as the between treatment comparisons displayed in the CER. In other words, the values shown in a proposed Table of the PI do not correspond with the primary efficacy results. This needed to be clarified by the sponsor.

Updates of studies previously evaluated by the TGA

The dossier included two CSRs (CS8663-A-U301 and CS8663-A-E303) which had previously been evaluated by the TGA as part of the submission for Sevikar (OM/AML) but the study reports in each case only provided data to week 10 for that prior evaluation. The full study reports were available for this evaluation.

Study CS8663-A-U301 was a randomised, factorial, 8 week study evaluating the efficacy and safety of co-administered OM and AML compared to monotherapy in 1400 adults with mild to severe hypertension (mean baseline BP of 163.6/101.5 mmHg). The dossier included the CSR for Period III of the trial which was an open label, 44 week (week 8 to 52) extension study. There were 1684 subjects who entered the extension and were treated with OM 40 mg + AML 5 mg. The latter was uptitrated to AML 10 mg if their BP was not adequately controlled. The addition of HCTZ 12.5 mg and then 25 mg was then offered for further BP control. There were 1400 (83%) subjects who completed the extension study. The blood pressure goal was <140/90 mmHg or <130/80 mmHg for diabetic patients. At week 52, there were 287 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg with a msDBP of 81.0 mmHg and a msSBP of 130.7 mmHg. Two thirds (67%) of these subjects had reached their BP goal. There were 419 subjects on OM 40 mg + AML 10 mg + HCTZ 25 mg with a msDBP of 83.4 mmHg and a msSBP of 136.8 mmHg with 46.3% reaching BP target.

Study CS8663-A-E303 was a Phase III randomised, 52 week study of add-on olmesartan in 755 adults subjects with moderate to severe hypertension inadequately controlled on AML 5 mg. The first three periods of the study were 8 weeks each and were: open label AML; double blind fixed dose; and double blind with dose titration. The dossier included the CSR for Period IV of this study which covered a 28 week open label extension (weeks 24 to 52) in 692 subjects. In this period, subjects received OM 40 mg and AML 5 mg which could be uptitrated to AML 10 mg. After this HCTZ 12.5 mg and then 25 mg could be added if required. Uptitration was required for msSBP/DBP ≥140/90 mmHg. For the 692 subjects in Period IV, the baseline msBP (start of randomised treatment at week 8) was 154.5/97.0 mmHg. The completion rate of Period IV was high (97%). At week 52 after three possible titration steps, 67% of subjects had reached the BP target. At this time, 68 subjects were on OM 40 mg + AML 10 mg + HCTZ 12.5 mg with a msSBP/msDBP of

138.3/87.3 mmHg and 47.1% had reached the BP goal. There were a further 27 subjects on OM 40 mg + AML 10 mg + HCTZ 25 mg with a msSBP/msDBP of 145.6/89.7 mmHg and 9 (33.3%) reached the BP goal.

Delegate's comments: Although these two studies do offer some evidence of the add-on effect of HCTZ, it can only be supportive. Addition of HCTZ was not assessed in these studies in any double-blind fashion but in open-label extensions. The sponsor was invited to submit further analyses which examine the actual add-on effect of HCTZ in those patients who had HCTZ added as a third active on top of the dual combination of OM + AML compared with the situation in those same patients before the addition of the HCTZ. Furthermore, neither study examined the add-on effect of either olmesartan or amlodipine to the corresponding dual therapy.

Other studies in the dossier

Study SP-OLM-03-05 was a 22-week, Phase IV, open label, non-comparative, multicentre study of OM and an sequential add-on treatment of HCTZ and amlodipine in 694 subjects with mild to moderate hypertension. The primary objective was to evaluate the rate of subjects treated to target (STTT) overall and at each combination treatment step. The target BP (at trough) was msSBP ≤130 mmHg and msDBP ≤85 mmHg for non-diabetics and msSBP <130 mmHg and msDBP <80 mmHg in diabetics. Subjects were adults with mild to moderate essential hypertension with msSBP ≥140 and <180 mmHg and/or msDBP ≥90 and <110 mmHg.

After a 2 week placebo run-in period, there were 5 active treatment periods of 4 weeks duration each. If the entry criteria were met, subjects were treated with the following sequential steps:

- 20 mg OLM once daily (od);
- 20 mg OLM + 12.5 mg HCTZ (fixed combination) od;
- 20 mg OLM + 25 mg HCTZ (fixed combination) od;
- 20 mg OLM + 25 mg HCTZ (fixed combination) plus 5 mg AML od;
- 20 mg OLM + 25 mg HCTZ (fixed combination) plus 10 mg AML od.

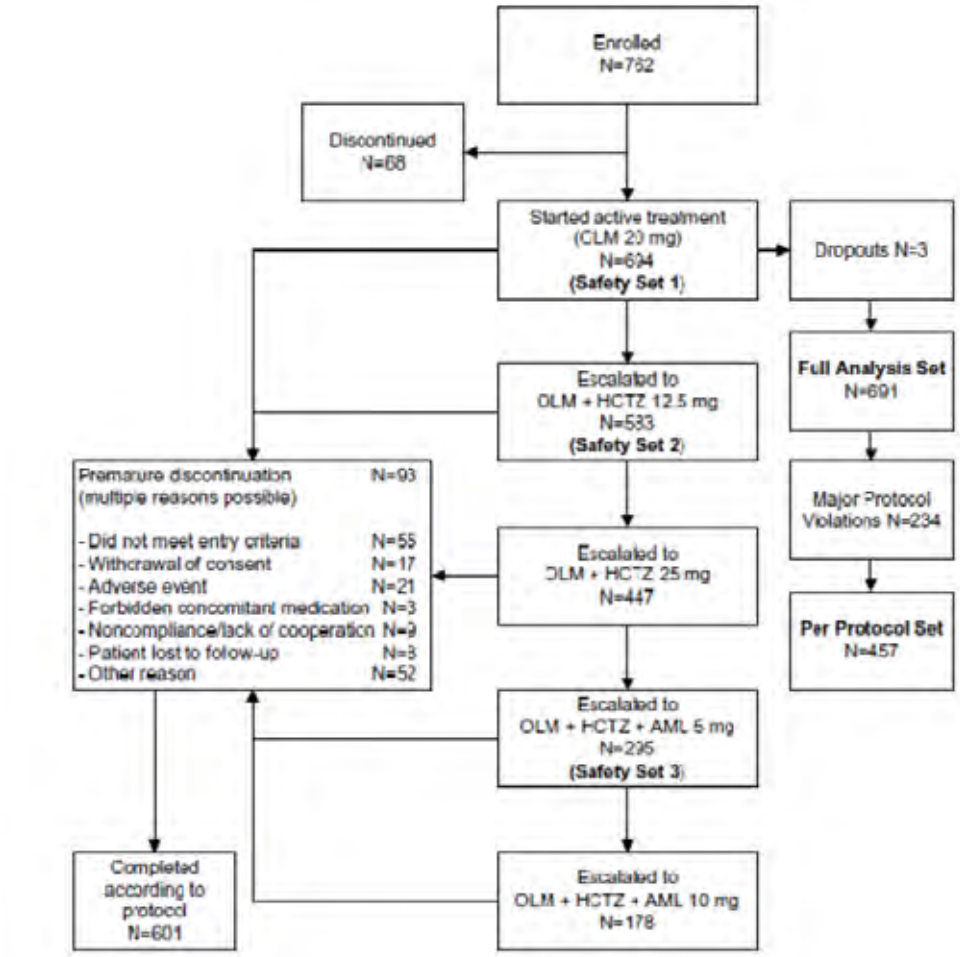
There were 762 subjects enrolled and 694 who commenced study treatment with 691 subjects (90.7%) in the FAS and 457 (60.0%) in the PP set. There were 103 subjects who received the triple combination of OM/HCTZ/AML 20/25/5 mg and 59 who received OM/HCTZ/AML 20/25/10 mg.

In the FAS the rate of subjects treated to target was 71.8% (95% confidence interval (CI): 68.4, 75.1%) and in the PP set the rate was 84.5% (95% CI: 81.1, 87.8%). The proportion of subjects attaining target BP was 12.3% with monotherapy OM 20 mg, 16.4% with dual therapy OM/HTCZ 20/12.5 mg, 19.2% with dual therapy OM/HTCZ 20/25 mg, 14.9% with triple therapy OM/HTCZ/AML 20/25/5 mg and 8.5% with triple therapy OM/HTCZ/AML 20/25/10 mg. From a baseline msSBP/msDBP of 158.1/94.7 mmHg, there was a mean change to the last available assessment of –29.6/-15.7 mmHg.

Delegate's comments: Again the evidence for add-on therapy, this time of AML, is supportive only because it was assessed in an open-label context only and not in a double-blind manner. It was reassuring to see at each of the 4 add-on steps progressively more people achieving target blood pressure. The comparisons are indirect. It is not possible to perform any formal comparisons of blood pressure reductions at each stage. However, the Delegate requested the sponsor to do some limited comparisons. Referring to Figure 7 below, there were 694 subjects who were commenced on active treatment with OM 20 mg. Of these, 447 had their regimens escalated to OM 20 mg + HCTZ 25 mg, that is, to the dual therapy step before escalation to triple therapy. Of these 447, 133 achieved their target BP

(133/447 or 29.8%; 133/694 or 19.2% of those commenced on active treatment). Thereafter, of the same 447, 295 were escalated to the first triple therapy option of OM 20 mg + HCTZ 25 mg + AML 5 mg and of these 295, 103 achieved their target BP (103/295 or 34.9%; 103/694 or 14.8% of those commenced on active treatment). Finally, of these 295, 178 were escalated to the next step up in triple therapy of OM 20 mg + HCTZ 25 mg + AML 10 mg. Of this final group of 178, 59 achieved their target BP (59/178 or 33.1%; 59/694 or 8.5% of those commenced on active treatment).

Figure 7. Study SP-OLM-03-05. Disposition of patients.



The sponsor was requested to produce a detailed summary of the disposition or flow of patients for the one step from OM 20 mg + HCTZ 25 mg to the first triple therapy combination of OM 20 mg + HCTZ 25 mg + AML 5 mg. There were 447 patients at the beginning of this step. Similarly, the Delegate requested the sponsor to produce a detailed summary of the disposition of patients for the one step from the first triple therapy combination of OM 20 mg + HCTZ 25 mg + AML 5 mg to the next triple therapy combination of OM 20 mg + HCTZ 25 mg + AML 10 mg (295 patients at the beginning of this step) as well as a detailed summary of the disposition of the 178 patients whose regimen was escalated to OM 20 mg + HCTZ 25 mg + AML 10 mg. The latter disposition is to be until study end. For the 295 patients whose regimen was escalated from the dual combination of OM 20 mg + HCTZ 25 mg to OM 20 mg + HCTZ 25 mg + AML 5 mg, the sponsor was requested to produce details of both the msDBP and msSBP at the beginning and end of the 4-week period during which the AML 5 mg was able to exert its add-on effect as well as the extra proportion of subjects achieving target BP (that is, the first addition of any AML). Likewise, for the 178 patients whose regimen was escalated from the first triple therapy option to the second triple therapy option, the sponsor was

requested to produce details of the msDBP and msSBP at the beginning and end of the 4-week period during the extra AML 5 mg was able to exert its add-on effect as well as the extra proportion of subjects achieving target BP in this last 4 weeks (that is, the second addition of the AML). Again the analyses are to be conducted on the data for those subjects actually exposed to the add-on of the third agent. Without these analyses there is no information about any actual add-on effects.

Safety

In the pivotal study Safety set 2, there were 574 subjects exposed to triple therapy for a mean duration of 53.6 days. Due to study design the mean duration of exposure to dual therapy was longer (82.7 to 83.0 days). In the Phase III open label cohort (uncontrolled extensions of Studies CS6883-A-U301 and -E303), there were 829 subjects who received OM 40/AML 10/HTCZ 12.5 mg for a mean duration of 111.6 days and 468 who received OM 40/AML 10/HTCZ 25 mg for mean duration of 175.0 days. The mean exposure to dual therapy AML 10/HCTZ 25 was 79.5-100.9 days. Due to the difference in duration of exposure, comparisons between triple and dual therapy group rates are not directly possible. In the Phase IV study, 294 subjects received triple combination (OM 20/AML 10/HTCZ 12.5 mg or OM 20/AML 10/HTCZ 25 mg) for a mean duration of 45.6 days.

Over the 12 weeks of the pivotal study, the rate of TEAEs was 58.4% in the triple combination group compared to 51.7% to 58.9% in the dual combination groups. In the triple combination group, the severity of TEAEs was generally mild (31.9%) or moderate (22.3%) with severe TEAEs being less frequent (4.2%). Similar proportions were seen across the dual therapy groups. In the triple therapy group, the most frequent system organ classes (SOCs) involved were nervous system disorders (19.3%), infections and infestations (14.8%) and general disorders and administration site conditions (15.9%). These rates were no greater than in the dual therapy groups. The most common TEAEs in the triple compared to dual therapy groups were dizziness (11.3% versus 3.4-10.7%), oedema (7.7% versus 1.6-9.8%), headache (6.4% versus 6.0-7.0%) and fatigue (4.2% versus 5.3-6.5%).

In the pivotal study treatment-related TEAEs were reported in 28.2% of the triple therapy compared to 20.9-29.7% of the dual therapy groups. The most frequent treatment-related TEAEs were dizziness (6.4%), peripheral oedema (6.1%) and headache (3.0%). These rates were no higher than for any dual combination group. The rate of hypotension was greater with the triple than dual therapies (1.2% versus 0-0.3%), as was increased creatinine (1.2% versus 0-0.5%). The rates of treatment-related hypokalaemia were 0.5% versus 0.2-3.4% in the triple and dual therapy groups, respectively. Most treatment-related events were mild or moderate. Severe treatment-related TEAEs occurred in 1.2% of subjects in the triple therapy compared to 0.4-1.5% in the dual therapy groups. In the Phase III open label cohort, the rate of treatment-related TEAEs with triple therapy was 24.3% which was higher than dual therapy OM/AML (11.1%-15.1%). Most were mild (16.6%) or moderate (7.4%) with only 2 (0.2%) severe treatment-related TEAEs both of which were in subjects who received OM 40/AML 10/HCTZ 12.5 mg. The most frequent events were peripheral oedema (10.5%), oedema (2.5%), dizziness (2.8%), hypotension (1.7%), increased blood creatinine (1.0%) and pollakiuria (1.2%). There was an increased risk of renal impairment TEAEs with triple therapy (2.1% versus 0.2-1.3%).

There was one death in CS8635-A-U301. This subject was on AML 10 mg / HCTZ 25 mg and died prior to week 4 from 'alcohol poisoning' and was not included in Safety set 2. There was one death in the Phase III open label cohort. This subject on OM 40 mg + AML 10 mg died from a gunshot wound. There were no deaths in the Phase IV study.

In the pivotal study the rate of SAEs while taking triple therapy was 1.6% (n=9) compared to 1.3% to 1.8% while taking a dual therapy and 2.8% while on placebo. There was one

subject in the triple therapy group who discontinued the study due to an SAE (coronary artery disease). There were three treatment-related SAEs in two subjects (angina pectoris in a subject on OM 40/AML 10 mg and acute renal failure and syncope in a subject on AML 10/HCTZ 25 mg) neither of whom were on triple therapy. The rate of SAEs in the Phase III open label cohort was 1.8% and 3.8% for subjects while taking OM 40/AML 10/HCTZ 12.5 mg and OM 40/AML 10/HCTZ 25 mg, respectively. The SAE rate while on OM 40/AML 5 mg and OM 40/AML 10 mg was 1.8% for each. The SAEs which resulted in discontinuation is subjects treated with triple therapy included: hepatic malignant neoplasm, psychotic disorder, chest pain, dizziness and small intestine obstruction. There were seven (1.0%) SAEs in the phase IV study (cellulitis, rectal cancer, acute myocardial infarction, myocardial infarction, lung disorder, inguinal hernia, and spinal osteoarthritis). None of the SAEs was considered treatment-related.

The discontinuation rate from double-blind treatment due to AEs in the pivotal study was 7.7% with triple therapy compared with 3.5%, 7.2% and 6.3% for the dual combinations of OM 40/AML 10 mg, OM 40/HCTZ 25 mg and AML 10/HTCZ 25 mg, respectively. There were 4 discontinuations due to severe treatment-related TEAEs: one due to dizziness in the OM 40/AML 10 mg group; one due to nausea in the AML 10/HCTZ 25 mg group; and one due to hyperkalaemia and one due to headache in the triple combination group. The most frequent TEAEs leading to discontinuation were dizziness (1.0% versus 0.2-0.3%), peripheral oedema (0.9% versus 0.2% both) and hypotension (0.7% versus 0-0.3%) in the triple versus dual therapy groups. The overall discontinuation rate due to AEs in the phase 3 open label cohort was 3.6%. The AE discontinuation rate while taking dual therapy was 1.4-1.5% and while taking OM 40/AML 10/HCTZ 12.5 mg was 1.3% and for OM 40/AML 10/HCTZ 25 mg it increased to 2.5%. Events leading to discontinuation occurring in more than one subject on triple therapy included oedema and increased blood creatinine. In the Phase IV study, 2.7 % of subjects discontinued due to a TEAE, the most common of which was dizziness.

In the pivotal study the rate of increased potassium (>5.0 mmol/L) was no higher with triple therapy than with OM 40/AML 10 mg (5.9% versus 7.6%) and the rate of low potassium (<3.5 mmol/L) was similar to OM 40/HCTZ 25 mg (2.2% versus 2.4%) and less than with AML 10/HCTZ 25 mg (9.8%). There were 2 subjects with laboratory related SAEs: one hyperkalaemia in a subject on OM 40 /HCTZ 25 mg and one hypokalaemia and hyponatraemia in a subject on AML 10/HCTZ 25 mg. The rate of TEAEs of hyperkalaemia was slightly higher with triple therapy than with dual therapy (0.9% versus 0.3-0.5%). The rate of hypokalaemia TEAEs in the triple therapy group (1.6%) was slightly higher than in the dual therapy groups OM 40/AML 10 mg and OM 40/HCTZ 25 mg (0.5% and 1.0%, respectively). However, the highest rate of hypokalaemia TEAEs was seen in the AML 10/HCTZ 25 mg group (7.1%). In the Phase III open label cohort increased serum potassium rates were lower with triple than with dual OM/AML therapy (2.4-2.8% triple versus 4.5-5.3% dual). The rates for hypokalaemia in the Phase III open label cohort were as follows: 0.5% [OM 40/AML 5], 0.6% [OM 40/AML 10], 0.8% [OM 40/AML 10/HCTZ 12.5] and 7.5% [OM 40/AML 10/HCTZ 25]. A very large jump in the rate of hypokalaemic events in this cohort at the highest triple therapy dose was noted.

For the pivotal study the rates of increased creatinine > 1.4 mg/dL and of creatinine clearance ≤ 60 mL/min were 6.4% and 5.4%, respectively which were less than the corresponding rates in the OM 40/HCTZ 25 mg group, viz. 7.1% and 6.6%, respectively. The incidence of renal impairment AEs was greater with triple than with dual therapy (2.1% triple versus 0.2-1.3%). In the Phase III open label cohort, there were no clinically notable mean changes from baseline to week 12 in creatinine or blood urea. There were, however, 11.3% of subjects on the triple combination OM 40/AML 10/HCTZ 25 mg with creatinine >1.4 mg/dL compared to 1.3%-4.0% in the other groups (including OM 40/AML 10/HCTZ 12.5 mg which had the second highest rate of 4.0%). The rate of renal AEs was higher with triple therapy compared to the other groups (1.7% versus 0.1-0.7%).

The rates of glycaemic control events and gout, hyperuricaemia and increased uric acid events were no greater with the triple therapy than other groups. Electrocardiogram findings were unremarkable. There were small increases in liver function with marked elevation of ALT, AST and total bilirubin occurring in 1.3%, 2.7% and 0.2% of subjects respectively, though this was no greater than with dual therapy.

In the pivotal study the rate of SAEs in those treated with triple therapy was higher in the ≥65 years sub-group than in the <65 years sub-group (5.1% versus 0.9%). Likewise, in the ≥65 years sub-group, the rate of SAEs in those treated with triple therapy was higher than in those treated with dual therapy (5.1% versus 1.6-3.4%). Compared to those aged <65 years, the elderly on triple therapy had a higher rate of oedema (12.7% versus 6.4%), dizziness (11.8% versus 9.3%), renal impairment AEs (3.4% versus 1.8%) and hypotension (2.5% versus 2.0%). In the Phase III open label cohort, subjects aged ≥65 years treated with triple therapy had a TEAE rate of 64.5%, a treatment-related TEAE rate of 27.9%, a severe TEAE rate of 4.4%, an SAE rate of 8.2% and a rate of discontinuation due to an AE of 3.8%. As seen in the pivotal study, the risk of AEs was greater in the elderly than in those aged <65 years. The most frequent TEAEs were oedema (16.5% with OM 40 /AML 10/HCTZ 25 mg and 16.8% with OM 40/AML 10/HCTZ 12.5 mg) followed by dizziness (6.2% and 5.8%, respectively).

There were no new safety signals across sub-groups of gender, diabetes, hypertension stage and severity or BMI.

As noted by the clinical evaluator safety data from the 40-week extension of the pivotal study were not included in the original dossier. The data were provided in response to a TGA request for further information. The rates of AEs were highest with the highest dose of triple therapy, although the exposure duration to this dose was also greater. Adverse event-related discontinuations over the 40 week period remained relatively low indicating treatment tolerance. Treatment-related SAEs were infrequent (0.2%).The AE profile was consistent with earlier data evaluated and no particular safety signals were evident.

PSUR data: As also noted by the clinical evaluator, the triple fixed-dose combination tablet has been approved in the USA since 2010. As part of the TGA request for further information, the clinical evaluator asked the sponsor to comment on the latest PSUR data. The sponsor advised that data relating to the triple combination has been included in the Olmetec PSURs since the 17th report. The most recent PSUR (the 21st PSUR, numbered 866-021 and dated 10 December 2012) had been submitted to the TGA and was also included in the sponsor's response to this question.

The sponsor maintained that the *Adverse Events* section of the Australian-approved PI had been kept up to date with all relevant safety information arising from this post-marketing data and that the amendments had been included in the PI under sub-headings for the individual components. The latest PSUR (21) reported an estimated patient exposure of 401,850 to the triple combination. There were 173 medically confirmed AE reports with the triple therapy with an ADR report rate of 4.3 per 10,000. Included in these reports were 20 serious cases and one death due to lactic acidosis and renal failure. The most frequent events reported were of oedema peripheral, nausea, dizziness, drug ineffective, oedema and pain in extremity.

Delegate comment: In the response to this Overview, the sponsor was requested to provide a detailed summary, in chronological order, of all amendments of a safety-related nature, made to the PI of any Australian-registered olmesartan-containing product which has specifically arisen from post-marketing reports of AEs associated with the use of the triple combination of OM, AML or HCTZ, whether in a free combination of 3 mono-therapies, a monotherapy and a dual therapy or the fixed-dose combination tablet of the 3 actives. The sponsor was also asked to detail whether, in reporting these new AEs "under sub-headings for the individual components", it has been made clear to the reader of the PI

that the AE has occurred in the context of exposure to the triple combination. For each of these new individual AEs requiring a safety-related amendment, a separate answer was required.

In the CER, the clinical evaluator also reported that following findings of increased cardiovascular deaths in two studies of OM in diabetic patients (ROADMAP and ORIENT), additional analyses regarding cardiovascular risks were performed. This issue was addressed by the sponsor in the response to the final CER. It appeared that there have been recent discussions between the sponsor and the European Authorities on cardiovascular risk which resulted in recommendations to include further data in the product information of OM-containing medicines. The sponsor confirmed that these discussions have focussed on the ROADMAP and ORIENT studies. At the time this Overview was prepared, the reports of these 2 studies were under review by the TGA OPR.

In the EU, the PRAC arrived at the following recommendations:

- The Marketing Authorisation Holder (MAH) for the originator of OM-containing products should submit a variation in order to update the product information to address the signal and provide additional clarification on some data included in their responses.
- A 60-day timetable was agreed for the assessment of this variation which will lead to a further PRAC recommendation.

The sponsor advised that a proposal for inclusion of wording in section 5.1 of the Summary of Product Characteristics (SmPC) for olmesartan containing products in the EU, reflecting the data on cardiovascular safety from the ROADMAP and ORIENT trials, has been submitted as a variation application. Final European texts of the SmPC will be available only after conclusion of this variation procedure and this is expected later this year. The sponsor has stated that it would continue to provide the TGA with further information as it becomes available.

Delegate comment: In the response to this Overview, the sponsor was requested to provide the latest update on this particular issue. In particular, the sponsor was requested to indicate whether or not a variation application has been submitted and to give precise details of the variation sought or applied for. Further relevant information about this issue of potential cardiovascular safety in people with diabetes appears in the next section dealing with the RMP, below.

Clinical recommendation

The clinical evaluator does not recommend approval of SEVIKAR HCT for the proposed indication, '*SEVIKAR HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy'* but rather for an indication covering substitution or replacement therapy.

Risk management plan

A RMP waiver for this application was granted by the OPR of the TGA at the application pre-submission assessment stage. In the final CER, the evaluator noted that PSUR 21 stated that the EU-RMP had been updated to include cardiovascular risk. The sponsor advised that this update to the RMP was in accordance with the request of the German regulatory authority (see above). The Delegate requested that in the response to this Overview the sponsor provide details about the manner in which the EU RMP has been updated with a statement on cardiovascular risk.

In the response to the final CER, the sponsor maintained that the cardiovascular signal realised in the ROADMAP and ORIENT studies was a chance finding. The sponsor further

stated that the signal has been thoroughly evaluated in 4 post-marketing investigations: nonclinical assays, an ICH E14 thorough QT study, a retrospective epidemiological database study, and a meta-analysis of clinical trials sponsored by Daiichi Sankyo [sponsor of the ROADMAP and ORIENT trials]. The sponsor concluded that these studies uniformly demonstrated that olmesartan does not pose a cardiovascular risk.

The Delegate considered there was a lack of clarity around this issue and requested the sponsor address this in the response to this Overview. In particular, if post-marketing studies have all concluded that there is no cardiovascular risk, why has the EU RMP been updated to include such a risk? Has the EU RMP been so updated? The sponsor was asked to provide a summary of the original findings in the ROADMAP and ORIENT studies which suggested the existence of such a risk, a summary of the 4 post-marketing studies and a discussion of how the data from the latter can overturn the findings of the former

Risk-benefit analysis

Delegate considerations

Bioequivalence issues

Based on the data presented in the dossier and on the comprehensive and detailed answers presented by the sponsor to all of the questions raised by the TGA in the request for further information, the Delegate was satisfied that all of the market formulations can be considered to be bioequivalent to their corresponding component formulations and that dose proportional PK can be assumed across the five proposed dosage strengths. The Delegate was satisfied that there is sufficient evidence to permit the establishment of bioequivalence between the various free combinations studied and the fixed-dose triple combination proposed for marketing.

Efficacy

The clinical evaluator has argued that the triple combination should only be used as third-line therapy as direct substitution (or replacement) for patients already controlled on a dual component and a single component formulation. The evaluator was of the opinion that there were insufficient clinical data to support an add-on therapy indication.

In its response to the final CER, the sponsor disagreed with the evaluator's comments on the proposed indication and stated that the evaluator seems to have misunderstood the proposed indication combined with the dosing instructions. The proposed indication reads *"Sevikar HCT is indicated for the treatment of hypertension. This fixed-dose combination is not indicated for initial therapy"*. The proposed dosing instructions are broken down into those for replacement therapy and those for add-on therapy.

The Delegate would agree with the sponsor that the dosing instructions do not propose that patients are to be switched from any single anti-hypertensive therapy directly to triple therapy. The proposed dosing instructions are based on the premise that a patient would be receiving dual therapy, that is, be currently on any two out of the three possibilities before initiation of the triple therapy, that is, as add-on therapy. However, the Delegate does not consider there has been any misunderstanding on the part of the clinical evaluator. The evaluator makes it clear that in his/her opinion, there is insufficient evidence to support an add-on indication but that there is sufficient evidence to support a substitution or replacement indication. In this regard, the Delegate was inclined to agree with the evaluator. Even if it was found that there was sufficient evidence to support an add-on indication, there is presently a major problem with the wording of that indication. It was extremely important that the wording of an indication convey a precise idea of the population targeted for treatment. It should be able to stand on its own and not be subject to possible misinterpretation. A reading of the proposed indication on its own does permit

the use of Sevikar HCT as the next step up from monotherapy. The dosing instructions do make an attempt to correct this first impression of being able to go from monotherapy to the triple combination Sevikar HCT. However, this means that a correct interpretation of the indication is dependent on a close reading of the dosing instructions. This situation could be partially remedied by re-wording of the indication to embed a brief summary of the dosing instructions plus a cross-link to those instructions. The dosing instructions would also need to be considerably tightened, firstly by pointing out that going from monotherapy straight to the triple combination is not appropriate and by use of the phrase 'dual combination' where relevant and by use of the word 'only', for example, by amending the introductory wording under Add-on therapy to: *'For use only in patients whose blood pressure is not adequately controlled on any of the dual combinations of olmesartan and amlodipine OR olmesartan and hydrochlorothiazide OR amlodipine and hydrochlorothiazide...'*.

Overview of the evidence presented

In the pivotal study, CS8635-AS-U301, the mean change from baseline to week 12 (LOCF) in msDBP was -21/5 mm Hg for the triple combination and -17.8 mm Hg, -16.5 mm Hg and -14.8 mm Hg for OLM 40/AML 10, OLM 40/HCTZ 25 and AML 10/HCTZ 25 mg groups, respectively. The reduction in msDBP was statistically significant in all groups ($p < 0.0001$). The dual-subtracted LS mean difference, that is, the triple minus dual LS mean difference, ranged from -3.8 to -6.7 mm Hg and was likewise statistically significant in each case ($p < 0.0001$). Secondary outcome measures were all supportive of the primary result, for example, statistically significant reductions in msSBP and statistically significantly higher proportions of subjects reaching their BP target at week 12 on the triple therapy compared with those on dual therapy. However, as noted above, there are no formal add-on comparisons available from the data-set, that is, that there are no formal comparisons of the results between week 4 and those at week 12. The primary efficacy endpoint is solely based on the parallel-group comparisons. The final group of 600 patients on triple therapy which is used as the comparator group is itself derived from 3 sources, the first from a HCTZ add-on strategy, the second from an AML add-on strategy and the third from an OM add-on strategy. From the time-line data available for msDBP, msSBP and for the proportion of patients achieving blood pressure goal, there are improvements with the commencement of triple therapy after 4 weeks. However, these are observations based upon the parallel-group results overall. The analysis is not actually looking solely at the subjects who have been genuinely subject to an add-on therapy going from the end of week 4 to the end of week 12, that is, the analysis is not actually comparing the effect of the add-on therapy in the same group of individuals both before and after that add-on therapy. This is critical to the notion of add-on therapy.

In the discussion and comments above, the Delegate identified the 3 groups of subjects, each containing 200 subjects who have been actually subject to add-on therapy, and requested the sponsor conduct appropriate post hoc analyses for each of those groups. At this stage, there is only indirect evidence of an add-on benefit from the pivotal study and that is clearly insufficient to support an add-on indication. Moreover, it is looking at a pooled add-on benefit. The add-on benefit of each of the three actives individually has not been subject to any critical or robust examination or analysis. The Delegate proposed to seek the views of the ACPM on this issue. The post hoc analyses may offer sufficient evidence to support an indication but until they have been presented and subjected to a critical examination, it is impossible to know. It would seem that the sponsor may have already done these analyses as the between-treatment comparisons summarised in a table in the proposed PI do not correspond with the primary efficacy results. This also needed to be clarified.

Another deficiency of the pivotal study is that, with regard to any possible actual add-on effect, the study only examined the following transitions (OLM/AML/HCTZ is the order of

dosage strengths in all cases): from 40/10/0 to 40/10/25, 40/0/25 to 40/10/25 and 0/10/25 to 40/10/25. Each of these 3 transitions involves a transition with an intermediate dosage strength which was not tested but which may have been sufficient to achieve target therapy (for example. 40/10/0 to 40/10/12.5 and so on). In other words, there may have unnecessary treatment at an unnecessarily high add-on dose. There were also no transitions studied at the lower ends of the dosage strength ranges in the pivotal study.

In each of the previously evaluated studies, CS8663-A-U301 and CS8663-A-E303, the actual dosage transitions studied were (again OLM/AML/HCTZ is the order of dosage strengths): from 40/10/0 to 40/10/12.5 and then from 40/10/12.5 to 40/10/25. No other transitions from dual to triple therapy were studied. It was shown that there was an extra proportion of subjects who achieved blood pressure control with the addition of hydrochlorothiazide (either 12.5 or 25 mg) in an open-label extension period. The Delegate requested the sponsor's response to the overview include the precise details of the extra proportions (both as percentages and as n/N) of subjects achieving blood pressure control with the addition of the first 12.5 mg of HCTZ and then with the addition of the next 12.5 mg of HCTZ. In each case, the sponsor was requested to calculate the mean drop in both msDBP and msSBP at each step. The Delegate was seeking a comparison in the same group of patients, a before add-on and an after add-on comparison of the relevant parameters in that group of patients given add-on HCTZ in going from dual to triple therapies or in going from the first to the second steps of triple therapy. As noted above, addition of HCTZ was not assessed in these studies in any double-blind fashion but in open-label extensions. Furthermore, neither study examined the add-on effect of either OM or AML to the corresponding dual therapy. The Delegate proposed to seek ACPM advice on this matter.

In the open-label, non-comparative, Phase IV study, SP-OLM-03-05, in 694 adults with mild to moderate hypertension, it was found that the target BP could be achieved in a total of 72% of subjects with a stepped algorithm of OM 20 mg, followed by the addition of HCTZ (first 12.5 mg and then an extra 12.5 mg), followed in turn by the addition of AML (first 5 mg and then an extra 5 mg). Thus this study potentially examined the add-on effect of AML in going from dual to triple therapy. The actual dosage transitions studied were (again OLM/AML/HCTZ is the order of dosage strengths): from 20/0/25 to 20/5/25 and then from 20/5/25 to 20/10/25 mg. At each step there appeared to be an increase in the proportion who did achieve target BP. However, as noted above, there are no formal analyses of the actual add-on effect of either the amlodipine 5 or 10 mg, in moving from dual to triple therapy or from the first to the second step of triple therapy, in those people exposed to that actual add-on therapy. Until these analyses are forthcoming, the Delegate was not in a position to recommend approval of either an add-on indication or the add-on dosing instructions. The Delegate proposed to seek ACPM comment on this issue. The Delegate also requested the sponsor supply those analyses in the response to the Overview.

Regulatory guidelines

The EU guidelines which address the requirements for fixed-dose combinations have been written largely with dual combinations in mind, that is, combinations of two active ingredients, which is why they refer to first- and second-line therapies. In this submission, there is no proposal for use of the triple fixed-dose combination as first-line therapy. In any case such use would not be appropriate. For second-line therapy of a fixed-dose combination of two actives, the guideline outlines the requirements for studies to examine both add-on therapy and parallel-group comparisons of the combination with the individual components. For a triple fixed-dose combination, the situation is obviously more complicated in that there a greater number of lower level combinations, mono and dual, which can theoretically be tested against the triple. However, the principle of

separation of the add-on from the parallel-group comparisons remains a logical requirement. The great deficiency of the data set in this dossier is the lack of any rigorous, robust or formal evaluation of the add-on effect in going from dual to triple therapy in those subjects actually subject to the add-on therapy. Also there is only limited data to support dosage transitions by add-on within established triple therapy, firstly from 40/10/12.5 mg to 40/10/25 mg (previously evaluated studies, CS8663-A-U301 and CS8663-A-E303) and secondly from 20/5/25 and to 20/10/25 (the new supportive study SP-OLM-03-05). No other dosage transitions within established triple therapy were studied. Furthermore, neither of the two transitions studied was examined within the pivotal study. The Delegate has requested the sponsor address a number of issues in the response to the Overview and also called for a number of further analyses to be performed to see if there is sufficient evidence to support the add-on indication. At this stage the Delegate was of the view that there is insufficient evidence to support the latter.

A summary of the dosage transitions actually studied is shown in Table 5.

Table 5. Possible transitions from dual to triple therapy and comment on whether there is data of any sort to support the dosage transition specified by the cell in question

Dual	Triple combination OLM/AML/HCTZ (i.e. in that order)							
	20/5/12.5	20/5/25	20/10/12.5	20/10/25	40/5/12.5	40/5/25	40/10/12.5	40/10/25
OLM20/AML5	**no**	**no**	n/a	n/a	n/a	n/a	n/a	n/a
OLM20/AML10	n/a	n/a	**no**	**no**	n/a	n/a	n/a	n/a
OLM40/AML5	n/a	n/a	n/a	n/a	**no**	**no**	n/a	n/a
OLM40/AML10	n/a	n/a	n/a	n/a	n/a	n/a	**yes**	**yes (2 studies)#**
OLM20/HCTZ12.5	**no**	n/a	**no**	n/a	n/a	n/a	n/a	n/a
OLM20/HCTZ25	n/a	**yes**	n/a	**yes not direct**	n/a	n/a	n/a	n/a
OLM40/HCTZ12.5	n/a	n/a	n/a	n/a	**no**	n/a	**no**	n/a
OLM40/HCTZ25	n/a	n/a	n/a	n/a	n/a	**no**	n/a	**yes#**
AML5/HCTZ12.5	**no**	n/a	n/a	n/a	**no**	n/a	n/a	n/a
AML5/HCTZ25	n/a	**no**	n/a	n/a	n/a	**no**	n/a	n/a
AML10/HCTZ12.5	n/a	n/a	**no**	n/a	n/a	n/a	**no**	n/a
AML10/HCTZ25	n/a	n/a	n/a	**no**	n/a	n/a	n/a	**yes#**

*This table does not show the transitions which have been examined within established triple dosage therapy. In any event there were only 2 such transitions, the first from 40/10/12.5 to 40/10/25 and the second from 20/5/25 to 20/10/25.

n/a – cells marked n/a are those where there would have been dosage transitions in 2 or more out of 3 actives & dosage transitions involving dosage strength reductions

results from pivotal study; in the cell marked as having results from 2 studies, one of those two was the pivotal study but it must be remembered that none of the results from the pivotal study examined the results of add-on therapy in each group of patients actually subject to the add-on therapy; these have been requested as *post hoc* analyses.

Down the left hand column in the Table above are listed the possible dual combinations of dosage strengths and across the top row are listed the possible triple combinations of dosage strengths. The Delegate was interested only in those cells which involve a dosage transition of one, at most two intermediate dosage strengths, in the one active, for example, from OLM 20/AML 5 to OLM 20/AML 5/HCTZ 12.5 or to OLM 20/AML 5/HCTZ 25 but not to OLM 40/AML 5/HCTZ 25 or to OLM 40/AML 10/HCTZ 12.5 or to OLM 40/AML 10/HCTZ 25. The transition must also involve one from a dual to a genuine triple therapy. There are a large number of cells marked n/a as they involve dosage transitions in more than one active or may involve dosage strength reductions. Table 5 does not have cells which represent data to support dosage transition within established triple therapy. There are 18 cells which report 'no', that is, there is no data available of any sort to support the corresponding dosage transition. By comparison there are only 6 cells for which there is available data, that is, data to support the corresponding dosage transition. One of those cells, the cell for the transition from OLM/AML/HCTZ 40/10/0 to 40/10/25, does have data available from 2 studies, one of which was the pivotal study. There is a paucity of evidence for the low and intermediate dosage strength ranges and the Delegate regarded this as a great deficiency of the data-set.

Safety and RMP

There were greater rates of hypotension, dizziness, vertigo and syncope on triple therapy than on dual therapy and also a slightly higher rate of discontinuation due to AEs. Renal impairment AEs also occurred at a higher rate on triple compared with dual therapy. As noted by the clinical evaluator, triple therapy should be used with caution in patients with renal impairment. Its use is contraindicated in those with severe renal impairment. Other frequent events were oedema, headache, nausea, fatigue, hyperkalaemia and hypokalaemia. Oedema was associated with AML 10 mg but was not greater with the combination of AML 10 mg/HCTZ 25 mg.

In the pivotal study the rate of SAEs in those treated with triple therapy was higher in the ≥65 years sub-group than in the <65 years sub-group (5.1% versus 0.9%). Likewise, in the ≥65 years sub-group, the rate of SAEs in those treated with triple therapy was higher than in those treated with dual therapy (5.1% versus 1.6-3.4%). Compared to those aged <65 years, the elderly on triple therapy had a higher rate of oedema (12.7% versus 6.4%), dizziness (11.8% versus 9.3%), renal impairment AEs (3.4% versus 1.8%) and hypotension (2.5% versus 2.0%). In the Phase III open label cohort, subjects aged ≥65 years treated with triple therapy had a TEAE rate of 64.5%, a treatment-related TEAE rate of 27.9%, a severe TEAE rate of 4.4%, an SAE rate of 8.2% and a rate of discontinuation due to an AE of 3.8%. As seen in the pivotal study, the risk of AEs was greater in the elderly than in those aged <65 years. The most frequent TEAEs were oedema (16.5% with OM 40/AML 10/HCTZ 25 and 16.8% with OM 40/AML 10/HCTZ 12.5) followed by dizziness (6.2% and 5.8%, respectively).

All of the above imbalances with regard to the rates of AEs associated with triple therapy must be explicitly and transparently acknowledged in the PI. Despite these imbalances, there is no particular safety-related signal which would be sufficient to recommend rejection of the submission.

Indications

The Delegate strongly agreed with the clinical evaluator that there is insufficient evidence to support any recommendation for an add-on indication. There is only sufficient evidence to support a substitution or replacement indication. The Delegate proposed the following wording:

> *'SEVIKAR HCT is indicated for the treatment of hypertension. This triple fixed-dose combination is only indicated for those patients already stabilised on the combination of olmesartan medoxomil, amlodipine and hydrochlorohthiazide taken*

as separate tablets containing the same component doses of the three active ingredients.'

Proposed action

The Delegate proposed to reject the submission by Merck Sharp & Dohme (Australia) Pty Limited to register the triple fixed-dose combination tablet Sevikar HCT containing OM, AML and HCTZ in various dosage strength combinations, for the indication *SEVIKAR HCT is indicated for the treatment of hypertension. The fixed dose combination is not indicated for initial therapy*, and proposed instead to approve it for a substitution or replacement indication only.

This recommendation was based on an assessment of the efficacy of the product, particularly that relating to add-on therapy, not having been satisfactorily established for an indication which includes add-on therapy. However, the Delegate was of the view that the evidence presented so far was sufficient to recommend approval of the more limited substitution or replacement indication for the reasons stated above in the *Risk-Benefit Analysis* above and subject to provision of a PI and CMI acceptable to the TGA.

The recommendations of the clinical evaluator with respect to the PI are to be implemented (except that relating to the specific wording of the indications where the delegate has proposed his own version).

'SEVIKAR HCT is indicated for the treatment of hypertension. This triple fixed-dose combination is only indicated for those patients already stabilised on the combination of olmesartan medoxomil, amlodipine and hydrochlorohthiazide taken as separate tablets containing the same component doses of the three active ingredients.'

Request for advice

The Delegate proposed to seek advice on this application from the ACPM and in particular to request discussion of the following issues:

1. Does the ACPM agree with the Delegate that there is insufficient evidence at this stage to support an add-on indication but only sufficient evidence to support a replacement or substitution indication?
2. The Delegate seeks general advice from the ACPM as to what it considers to be a satisfactory level of evidence to support an add-on therapy indication for a triple therapy fixed-dose combination anti-hypertensive product. The Delegate also seeks advice on the appropriate context of such add-on therapy for a triple fixed-dose combination. For example, should consideration only be given to add-on therapy in moving from a dual combination to the triple combination or would there be situations where one could consider add-on therapy where the transition is from monotherapy to the triple therapy?
3. Having had an opportunity to view the sponsor's response to the Delegate's Overview, in which the sponsor was requested to provide further analyses of specific add-on effects as well as other data, is the ACPM now of the view that there is sufficient robust evidence of efficacy to permit an indication with an add-on component?

Response from sponsor

Merck Sharp & Dohme (Australia) Pty Limited (MSD) seeks approval to register SEVIKAR HCT, a triple therapy fixed-dose combination of OM, AML and HCTZ for the treatment of hypertension. The FDC is not intended for initial therapy.

MSD supports the Delegate's proposal to approve the indication for substitution or replacement therapy. However, MSD does not concur with the Delegate's proposal to reject the indication for add-on therapy as MSD considers that sufficient data have been submitted to support an indication for add-on therapy and therefore wishes to pursue the original wording of the Indication and not the amendment proposed by the Delegate.

MSD addressed the issues for which the Delegate sought ACPM advice:

1. There is insufficient evidence to support an add-on indication

MSD does not concur with the Delegate's proposal to reject the indication for add-on therapy and contends that there is sufficient evidence to support this indication from the submitted data:

a) Study CS8635-A-U301

This was a Phase III, multicentre, randomised, parallel group study. There were 3 periods: Period I was a 3-week wash out; Period II was a 12-week double-blind treatment period and Period III was a 40-week open label treatment period and 2-week follow-up. In Period II subjects were randomised to dual therapies (OM 40 mg + AML 10 mg + Placebo; OM 40 mg + Placebo + HCTZ 25 mg; Placebo + AML 10mg + HCTZ 25mg) by end of Week 4. At Week 4, 25% of subjects in each treatment group were switched to triple therapy while 75% of the subjects remained on the dual therapy.

Period II: The primary objective was to determine if the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg had a clinically significant benefit versus the respective dual therapy components in controlling BP after 12 week of treatment. The primary efficacy outcome, the mean reduction of sDBP from baseline to Week 12 (with LOCF) for triple therapy, was statistically greater than dual therapy ($p<0.0001$; Table 6). The LS mean difference between triple therapy and the three dual therapy groups ranged from -3.8 to 6.7 mmHg ($p<0.0001$). Results from secondary efficacy outcomes (including the msSBP and percentage of subjects reaching BP goal at Week 12) were consistent with the primary efficacy outcome. In particular, statistically greater ($p<0.0001$) proportion of subjects (64.3%) treated with triple therapy reached BP goal compared to the dual therapy groups (34.9–46.6%).

Table 6: Efficacy Parameters for Study CS8635-A-U301

	OM 40 mg + AML 10 mg + HCTZ 25 mg N=614	OM 40 mg + AML 10 mg N=624	OM 40 mg + HCTZ 25 mg N=627	AML 10 mg + HCTZ 25 mg N=593
Mean Change sDBP from baseline to Week 12	-21.5mmHg	-17.8 mmHg	-16.5mmHg	-14.8mmHg
Mean Change sSBP from baseline to Week 12	-38.1mmHg	-31.1mmHg	-31.2mmHg	-28.9mmHg
% achieving BP goal at Week 12	64.3%	46.0%	46.6%	34.9%

Results from this study clearly demonstrate that Triple Therapy provides additional clinical benefit in lowering BP compared to dual therapy and support the add-on indication for Sevikar HCT.

However, the Delegate expressed concern that there are no formal comparisons of the results between Week 4 (where all subjects were treated with dual therapy prior to randomisation) and Week 12, and requested the sponsor to conduct post hoc analysis. The sponsor is of the opinion that it was appropriate to conduct the efficacy analysis compared to baseline, instead of Week 4, as Week 4 was an interim time point in the study to ensure that all patients could tolerate dual therapy before being randomised/treated with triple therapy or dual therapy. Furthermore, the sponsor is also of the opinion that it was

appropriate to pool the data from all subjects receiving triple therapy despite the components of the previous dual therapy, as this was a double-blind and controlled study.

To address the concern of the Delegate, the analysis comparing Week 12 to the Week 4 data was performed. This analysis was conducted for non-responders (subjects who did not reach blood pressure goal [<140/90 mmHg or <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease]) and responders (subjects who reached blood pressure goal) at Week 4. The results obtained are summarised below (Table 7).

Table 7. Study CS8635-A-U301 – Change in sDBP and sSBP (mmHg) from Week 4 to Week 12 with LOCF and Percentage of Subjects Reaching Blood Pressure Goal at Week 12 with LOCF – Non-Responders and Responders at Week 4

	Week 4: OM40/AML10		Week 4: OM40/HCTZ25		Week 4: AML10/HCTZ25	
Parameter Statistics	Week 12: OM40/ AML10	Week 12: OM40/ AML10/ HCTZ25	Week 12: OM40/ HCTZ25	Week 12: OM40/ AML10/ HCTZ25	Week 12: AML10/ HCTZ25	Week 12: OM40/ AML10/ HCTZ25
Non-responders at Week 4						
N	332	96	311	98	356	132
Mean Change sDBP (SD)	-2.6 (8.83)	-8.3 (9.53)	-3.4 (9.51)	-7.5 (9.85)	-2.5 (7.51)	-7.6 (8.40)
Mean Change sSBP (SD)	-3.9 (13.23)	-16.7 (13.57)	-5.7 (16.60)	-11.9 (17.71)	-4.1 (11.93)	-13.6 (13.27)
% achieving goal	24.1%	57.3%	26.0%	52.0%	19.7%	50.8%
Responders at Week 4						
N	252	94	264	92	188	56
Mean Change sDBP (SD)	1.3 (7.85)	-2.7 (8.71)	1.7 (8.51)	-3.0 (7.92)	2.6 (7.91)	-3.5 (8.83)
Mean Change sSBP (SD)	2.2 (10.91)	-3.7 (13.33)	2.7 (13.27)	-2.5 (10.56)	3.5 (11.31)	-6.6 (12.55)
% achieving goal	77.8%	84.0%	72.7%	89.1%	68.6%	85.7%
% at goal at W4 and no longer at goal at W12	22.2%	16.0%	27.3%	10.9%	31.4%	14.3%

Results from the post hoc analysis showed that for non-responders at Week 4 who switched from a component dual therapy to triple combination therapy, additional mean reductions in sDBP and sSBP were observed from Week 4 to Week 12 compared to those who remained on a component dual therapy and resulting in greater proportion of subjects achieving BP goal. For responders at Week 4 who switched from a component dual therapy to triple combination therapy, additional mean reductions in sDBP and sSBP were also observed from Week 4 to Week 12 compared to those who remained on dual therapy, although to less extend compared to non-responders. The percentages of subjects remained at BP goal at Week 12 were higher in subjects who switched to triple therapy compared to those remained on dual therapy (Table above).

Period III: The effect of dosage transition in patients being treated with triple therapy was studied in the 40 week open label Period III (weeks 12 to 52) of the Sevikar HCT Study CS8635-A-U301, which was supplied to the TGA as part of the response to the TGA questions. This study also provided further information on the intermediate strengths of Sevikar HCT supporting dosage transitions by add-on therapy within established triple therapy.

After completing Period II all subjects were switched to OM 40/AML 5/HCTZ 12.5 mg. Those subjects who had not achieved blood pressure goal after 2 weeks of open-label treatment were randomly titrated to either to OM 40/AML 10/HCTZ 12.5 or OM 40/AML 5/HCTZ 25, together with a further titration to OM 40/AML 10/HCTZ 25 at the investigator's discretion. Subjects who achieved blood pressure goal remained on the same therapy throughout Period III., demonstrated maintenance of efficacy over 12 months when treatment was titrated to the maximal triple dose. The results are summarised below:

- Titration from OM 40/AML 5/HCT 12.5 to OM 40/AML 5/HCTZ 25 resulted in a mean reduction in sDBPof 2.9mmHg and a mean reduction in sSBP of 5.9mmHg.

- Titration from OM 40/AML 5/HCTZ 12.5 to OM 40/AML 10/HCTZ 12.5 resulted in a mean reduction in sDBP of 4.4mmHg and a mean reduction of sSBP of 6.8mmHg.
- Titration from OM 40/AML 5/HCTZ 25 to OM 40/AML 10/HCTZ 25 resulted in a mean reduction in sDBP of 5.7mmHg and a mean reduction in sSBP of 9.9mmHg.
- Titration from OM 40/AML 10/HCTZ 12.5 to OM 40/AML 10/HCTZ 25 resulted in a mean reduction in sDBP of 5.0mmHg and a mean reduction in sSBP of 10.2mmHg.

b) Study CS8663-A-U301

In the SEVIKAR Study CS8663-A-U301, Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of various treatment combinations. After completing Period II, all patients were switched to the combination of OM 40/AML 5. Those patients whose blood pressure was not adequately controlled on OM 40/AML 5 were titrated to OM 40/AML 10. Patients whose blood pressures were still not adequately controlled were offered HCTZ 12.5 or HCTZ 25, as required to achieve this blood pressure goal. Patients continued on this until Week 52. In order to address the concern of the Delegate, results of further specific add-on analyses for add-on HCT are summarised below:

- The mean changes in sDBP and sSBP were -4.8mmHg and -7.3mmHg, respectively, when the dosing regimen was titrated from OM 40/AML 5 to OM 40/AML 10.
- The mean changes in sDBP and sSBP were -4.5mmHg and -7.7mmHg, respectively, when the dosing regimen was titrated from OM 40/AML 10 to OM 40/AML 10/HCTZ 12.5.
- The mean changes in sDBP and sSBP were -6.0mmHg and -9.9mmHg, respectively, when the dosing was titrated from OM 40/AML 10/HCTZ 12.5 to OM 40/AML 10/HCTZ 25.

c) Study CS8663-A-E303

In the SEVIKAR Study CS8663-A-E303, Period IV consisted of a 28-week, open-label, long-term treatment. All patients initially received open-label OM 40/AML 5. If BP was not adequately controlled with this dose combination, investigators could titrate the doses first to OM 40/AML 10 and then to triple therapy with OM 40/AML 10/HCTZ (12.5 or 25) as required. In order to address the concern of the Delegate, results of further specific add-on analyses for add-on HCT are summarised below:

- Titration from OM 40/AML 10 to OM 40/AML 10/HCTZ 12.5 resulted in a mean reduction in sDBP of 6.3mmHg and a mean reduction in sSBP of 10.2mmHg.
- Titration from OM 40/AML 10/HCTZ 12.5 to OM 40/AML 10/HCTZ 25 resulted in a mean reduction in sDBP of 3.7mmHg and a mean reduction in sSBP of 3.8mmHg.
- After titration from OM 40/AML 5 to OM 40/AML 10, 80 (32.9%) patients reached BP goal.
- After titration from OM 40/AML 10 to OM 40/AML 10/HCTZ 12.5, 34 (37.8%) patients reached BP goal.
- After titration from OM 40/AML 10/HCTZ 12.5 to OM 40/AML 10/HCTZ 25, 7 (26.9%) patients reached BP goal.

d) Study SP-OLM-03-05

The OLMETEC Study [SP-OLM-03-05] was an open-label, non-comparative, sequential, add-on, multicentre trial in patients with mild to moderate hypertension, with a placebo run-in period of 2 weeks followed by up to 5 active treatment periods, each lasting 4

weeks. At the Delegate's request, the company has provided some comparisons of blood pressure reductions at the beginning and end of each stage. These are summarised below.

- Changes in sDBP were largest early in the study (baseline to Week 4: -6.44 ± 7.53 mmHg; FAS) and decreased to approximately half this effect at the later visits (-3.40 ± 6.84 mmHg and -3.47 ± 6.32 mmHg for Week 12 to Week 16 and Week 16 to Week 20, respectively; FAS).
- Changes in sSBP were largest early in the study (baseline to Week 4: -11.97 ± 11.42 mmHg; FAS) and decreased to approximately half this effect at the end (-6.79 ± 10.06 mmHg for Week 16 to Week 20; FAS).

e) Summary and conclusions

Table 8. Summary of efficacy studies

	OM40/AML5/HCTZ25		OM40/AML10/HCTZ12.5		OM40/AML10/HCTZ25	
	sDBP	sSBP	sDBP	sSBP	sDBP	sSBP
CS8635-A-U301 Period II (12 weeks)[1]						
From OM40/AML10					-4.5 mmHg	-8.4 mmHg
From OM40/HCTZ25					-5.4 mmHg	-8.1 mmHg
From AML10/HCTZ25					-5.4 mmHg	-7.6 mmHg
CS8635-A-U301 Period III (40 weeks)[2]						
From OM40/AML5/HCTZ12.5	-2.9 mmHg	-5.9 mmHg	-4.4 mmHg	-6.8 mmHg		
From OM40/AML10/HCTZ12.5					-5.0 mmHg	-10.2 mmHg
From OM40/AML5/HCTZ25					-5.7 mmHg	-9.9 mmHg
CS8663-A-U301 Period III(44 weeks)[2]						
From OM40/AML10			-4.5 mmHg	-7.7 mmHg		
From OM40/AML10/HCTZ12.5					-6.0 mmHg	-9.9 mmHg
CS8663-A-E303 Period IV(27 weeks)[2]						
From OM40/AML10			-6.3 mmHg	-10.2 mmHg		
From OM40/AML10/HCTZ12.5					-3.7 mmHg	-3.8 mmHg
SP-OLM-03-05 Period IV/V (4 weeks)[2,3]						
From OM20/HCTZ25	-3.40 mmHg	-7.48 mmHg				
From OM20/AML5/HCTZ25					-3.47 mmHg	-6.79 mmHg

1: Between-groups comparison
2: Within-groups comparison
3: Note that this study used 20 mg olmesartan for all treatment paradigms

In summary, the studies included in the marketing application as summarised in the above table were adequately support the add-on indication. These studies consists of blinded comparative study comparing dual versus triple therapy as well as open long-term study to better mimic the real use situation. MSD believes that these studies were appropriately designed to demonstrate that the addition of a third agent provides additional BP lowering effects compared to the dual therapy and that up titration within a triple therapy treatment paradigm also provides additional benefit. These results provide satisfactory evidence to support the add-on indication for a triple therapy fixed-dose combination anti-hypertensive product such as Sevikar HCT.

2) Dual to triple therapy or mono to triple therapy

MSD wishes to confirm that only dual to triple therapy is requested in this application.

The individual active ingredients of Sevikar HCT are already registered as individual products or in dual combination products for the treatment of hypertension (Olmetec, Olmetec Plus and Sevikar).

Sevikar is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled on either olmesartan monotherapy or amlodipine monotherapy. For patients whose blood pressure is not adequately controlled on the highest dose of Sevikar, the addition of HCTZ is recommended. Patients may thus already be receiving the triple combination as a dual-component formulation of Sevikar with a single-component formulation of HCTZ in free combination.

The complete data set demonstrates the improvement in blood pressure reduction when patients move from any dual combination, OM/AML, OM/HCTZ or AML/HCTZ, to the triple

combination. The dosing instructions for Sevikar HCT should therefore allow movement from any dual component therapy to the triple component therapy.

3) Other matters raised by the Delegate

- MSD advises that no safety related changes to any currently registered OM-containing product have occurred secondary to post-marketing AEs associated with the triple combination. Apart from anaphylactic reactions, which were added to olmesartan's core safety information around the international birth date of the triple combination [23 July 2010], the AEs listed in the post-marketing *Adverse Events* section have not changed for the core safety information or US Prescribing Information for olmesartan monotherapy or olmesartan in either of the dual combinations.
- Text describing the results of the ROADMAP and ORIENT studies is proposed to be added to Section 5.1 of the EU SmPC for all olmesartan-containing products. The type II variation will be submitted on 17 June 2013. It has been agreed between Daiichi Sankyo (the sponsor of all olmesartan-containing products in Japan, Europe and the US) and the European Authorities that the next update to the EU RMP in this regard is due only after conclusion of the planned type II variation. Full details of the proposed text to be included in the SmPC were provided to the TGA.
- The Phase III clinical trial design was determined by Daiichi Sankyo in consultation with the FDA. The FDA recommended a single study demonstrating that the antihypertensive effect of a triple combination is superior to those of each double combination at highest dosages, that is, OM 40/AML 10, OM 40/HCTZ 25 and AML 10/HCTZ 25. The FDA considered it acceptable that the highest dosages of the triple combination be used, but indicated that it needn't be the highest dosage.

Overall summary

- MSD contends the data submitted for evaluation, together with the additional post hoc analyses of the pivotal data and the additional summaries of the previously submitted data, to be a satisfactory level of evidence to support the add-on indication
- MSD contends that there are sufficient data to support both a substitution indication and an add-on indication and that the Indication should be for:

  The treatment of hypertension.
- MSD does not propose that treatment be initiated with the triple-component formulation.
- MSD contends that the dosing instructions for substitution therapy should allow patients receiving OM, AML and HCTZ from separate tablets to switch to Sevikar HCT tablets, that is, switch from three separate tablets or from a dual combination tablet and a single component tablet to Sevikar HCT tablets.
- MSD contends that the dosing instructions for add-on therapy should allow patients whose blood pressure is not adequately controlled on OM/HCTZ, OM/AML or AML/HCTZ therapy to be switched to Sevikar HCT tablets. Titration of the dosage is recommended.
- MSD contends that the *Dosage and Administration* section of the PI is the appropriate place to provide complex dosing instructions for substitution and add-on therapies, and not the *Indications* section as proposed by the Delegate.

Appendix to the sponsor's response

Issues raised in the Delegate's Overview but not discussed in the sponsor's response document (above) were addressed in an Appendix to the sponsor's response. The Appendix included the following information:

Delegate's request for information on the regulatory process for the FDC in the EU and Switzerland

Sponsor response:

The initial Marketing Authorisation Application submitted in the EU and Switzerland was identical to the application submitted to the TGA (that is, one pivotal SEVIKAR HCT study, Study CS8635-A-U301).

As part of the European development program for the Add-on Therapy indication, two additional SEVIKAR HCT studies were conducted:

- Study CS8635-A-E302
- Study CS8635-A-E303

MSD appreciates that these studies have not been evaluated by the TGA, however a brief description of these studies was provided [details not included here] for the benefit of the Delegate. Further details can be provided upon request.

Delegate's request for clarification of the values of the between-treatment comparisons in a proposed table of the PI

Sponsor response

The data supporting a proposed Table in the PI was sourced from a post-hoc analysis supplied to the FDA during evaluation of the New Drug Application. The data are now provided in the Appendix. MSD apologises that these data were not supplied to the TGA as part of the initial application.

Details of the sponsor's responses to other matters outlined in the Delegate's Overview, including results of the additional analyses requested by the Delegate, are not included in this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Sevikar HCT (containing olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide) to have an overall positive benefit–risk profile for the indication;

> *Sevikar HCT is indicated for the treatment of hypertension. This triple fixed-dose combination is only indicated for those patients already stabilised on the combination of olmesartan medoxomil, amlodipine and hydrochlorohthiazide taken as separate tablets containing the same component doses of the three active ingredients.*

The ACPM advised that, should the data discussed in the pre-ACPM response (and described in detail earlier in these minutes[11]) continue to be supportive of the add-on indication then the ACPM would support the indication as proposed by the sponsor. However, the ACPM was of the view that there should be very clear instructions in the PI about careful dosage titration.

Proposed conditions of registration:

The ACPM agreed with the delegate on the proposed conditions of registration.

Proposed PI/CMI amendments:

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Post ACPM considerations

Following the ACPM meeting, the Delegate invited the sponsor to submit any available additional (supplementary) data in support of the proposed indication for add-on therapy. The additional data was evaluated in a supplementary TGA report, summarised below.

Supplementary clinical data evaluation

This supplementary clinical evaluation report was prepared after the application was considered by the ACPM.

A summary of the supplementary clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Background

Supplementary data to the original submission has been provided by the sponsor in response to the Delegate's proposed action to reject the submission to register the triple FDC tablet Sevikar HCT containing OM, AML and HCTZ in various dosage strength combinations, for the indication *"Sevikar HCT is indicated for the treatment of hypertension. The fixed dose combination is not indicated for initial therapy".* The Delegate instead proposed to approve it for a substitution or replacement indication only. This recommendation was based on an assessment that the efficacy of the product had not been satisfactorily established for an indication which included add-on therapy.

Scope of the supplementary data

The supplementary data consisted of:

[11] In response to the Delegate's request for ACPM advice on whether there is insufficient evidence at this stage to support an add-on indication but only sufficient evidence to support a replacement or substitution indication, the ACPM was of the view that there is sufficient evidence to support the substitution indication. The evidence for the add-on indication is less certain. There is a cogent rationale and practical arguments in favour of the add-on indication from dual therapy only. The ACPM advised the Delegate to have the additional data discussed in the pre-ACPM response evaluated. Thus the sponsor should submit without delay the data submitted to the EMA for the add-on therapy indication (including at least the reports of the two studies, S8635-A-E302 & CS8635-AE303) and all data relating to the post hoc analysis supplied to the US FDA during evaluation of the New Drug Application. The data should be submitted for formal evaluation by the TGA. If these two collections of data also support the limited data in study CS8635-A-U301, then there may be sufficient evidence to support the add-on indication. However, the ACPM was of the view that there should be very clear instructions in the PI about careful dosage titration.

- Two pivotal randomised double-blind Phase III efficacy/safety studies (CS-8635-A-E302 and CS-8635-A-E303).
- Type II variation Final Variation Assessment Report [the EMA report]

Supplementary efficacy data

The two pivotal randomised, double-blind, Phase III studies evaluated the safety and efficacy of adding HCTZ to OM/AML combinations in subjects not adequately controlled on the dual-combination (CS8635-A-E303), and the additional effect of the OM/AML/HCTZ triple-combinations compared to the corresponding OM/AML dual-combination in subjects with hypertension (CS8635-A-E302). These data meet the requirements for evaluation of fixed-dose combinations as add-on antihypertensive therapy specified in the *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension* (CPMP/EWP/238/95 Rev 2).

The sponsor has stated that the submitted studies were conducted according to Good Clinical Practice guidelines and applicable regulatory requirements.

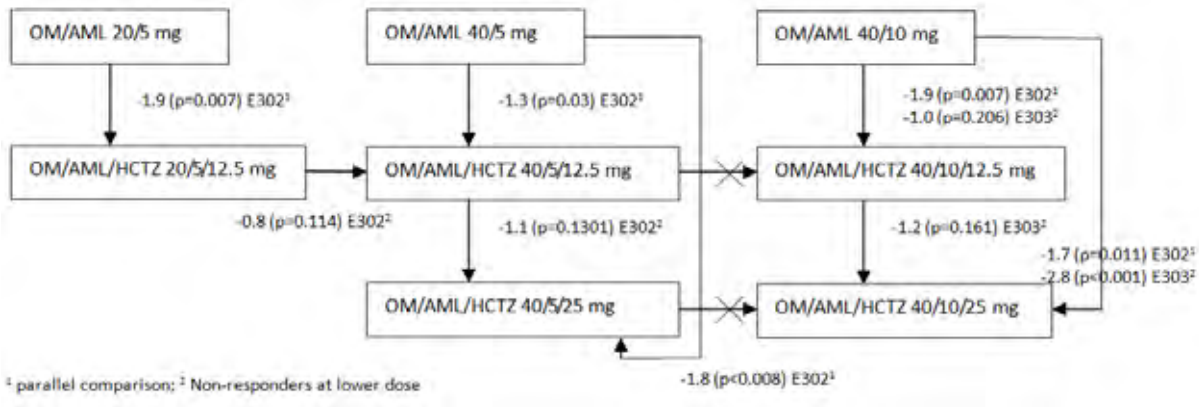
Evaluator's conclusions on clinical efficacy for add-on treatment of hypertension

The supplementary Studies CS8635-A-E302 and CS8635-A-E303 were submitted primarily to establish the efficacy of the triple combination product as add-on-therapy in subjects with moderate to severe hypertension.

Study CS8635-A-E303 is considered to more closely resemble the clinical situation because it compared the effects of adding HCTZ to OM/AML therapy in subjects who had not adequately responded to OM/AML therapy alone, whereas in Study CS8635-A-E302 subjects were randomised to dual or triple therapy irrespective of their response to dual therapy.

In both studies the primary efficacy endpoint was change in mean trough sDBP with LOCF, with change in mean trough sSBP and percentage achieving BP treatment goal being the most important secondary endpoints. Figure 8 below summarises the change in sDBP from both studies.

Figure 8. Summary of change in SeDBP at tested dose addition / titrations (Studies CS8635-A-302 and CS8635-A-303).



The results from Study CS8635-A-E303 demonstrated clinically meaningful differences in sDBP and sSBP reductions when subjects who were non-responders to OM/AML 40/10 mg had HCTZ 12.5 mg or 25 mg added to their dual combination therapy from Week 8 to Week 16 (Period II). The reduction in sSBP/sDBP in subjects who continued OM/AML 40/10 mg treatment during Period II was -6.9/-6.1 mmHg, compared with a reduction of -8.6/-7.1 mmHg in subjects who were randomised to OM/AML/HCTZ 40/10/12.5 mg, and

a reduction of -10.5/-8.9 mmHg in subjects who were randomised to OM/AML/HCTZ 40/10/25 mg. The sSBP/sDBP LS mean treatment difference was statistically significant between subjects who remained on OM/AML 40/10 mg and those who had their dose up-titrated to OM/AML/HCTZ 40/10/25 mg (-3.6/-2.8 mmHg, p<0.0001), but not in those who had their dose up-titrated to OM/AML/HCTZ 40/10/12.5 mg (-1.8/-1.0, p=0.0777/p=0.2062). These results are supported by the 24 h ABPM results, which demonstrated that subjects on either triple combination therapy had statistically and clinically meaningful differences in sSBP/sDBP compared with subjects who continued OM/AML 40/10 mg (-3.2/-1.9 [p=0.002/p=0.0018] and -4.6/-3.2 mmHg [p<0.0001] in subjects on OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg, respectively). Similar results were also obtained for daytime and night-time ABPM. Further support is provided by the percentage of subjects who reached their BP treatment goal, which was higher in subjects receiving OM/AML/HCTZ 40/10/12.5 mg (29.5%) and OM/AML/HCTZ 40/10/25 mg (41.3%) than in those remaining on OM/AML 40/10 mg (24.2%). Results were consistent across subgroups of age, gender, BMI, diabetic status, and hypertension severity. Although the study did not investigate the benefits of adding HCTZ to OM/AML 20/5 mg or OM/AML 40/5 mg, this was previously discussed with the European Authorities who stated: "If the benefit of add-on therapy is demonstrated using the highest doses of the baseline 2-drug therapy, then it can be assumed that benefit would also result from addition of the third component to lower doses of the 2-drug combinations".

Study CS8635-A-E302 provided supportive evidence from a parallel group comparison, with the triple therapy combinations of OM/AML/HCTZ 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, or 40/10/25 mg resulting in statistically significant greater LS mean reductions in sDBP/sSBP (of approximately 2/3 mmHg) and a higher proportion of subjects reaching their BP treatment goal (52–59%) compared to the respective dual component therapies (43–50%).

The case for the addition of OM to AML/HCTZ or AML to OM/HCTZ was addressed in the parallel group Study CS8635-A-U301 (evaluated in the original submission) that explored the following dual versus triple therapy comparisons in hypertensive subjects who were randomised to dual or triple therapy irrespective of their response to dual therapy:

- OM/AML 40/10 mg versus OM/AML/HCTZ 40/10/25 mg
- OM/HCTZ 40/25 mg versus OM/AML/HCTZ 40/10/25 mg
- AML/HCTZ 10/25 mg versus OM/AML/HCTZ 40/10/25 mg

It demonstrated a statistically significant mean difference between each triple therapy and the dual therapy groups for sDBP (-3.8 to -6.7 mmHg, p<0.001), sSBP (-7.1 to -9.6 mmHg, p<0.001), and proportion of subjects reaching their BP treatment goal (64.3% versus 34.9 to 46.6%, p<0.0001). This study also conducted an exploratory analysis of the BP outcomes in subjects who were non-responders at Week 4 on dual therapy. Non-responders switched to triple therapy had greater reductions in sDBP/sSBP (-7.5 to -8.3 mmHg / -11.9 to -16.7 mmHg) compared with those remaining on dual therapy (-2.5 to -3.4 mmHg / -3.9 to -5.7 mmHg), and a higher proportion of subjects who reached BP goal (50.8 to 57.3% versus 19.7 to 26.0%). While this was only an exploratory endpoint, the results for the OM/AML versus OM/AML/HCTZ comparison are consistent with those from Study CS8635-A-E303. It therefore seems not unreasonable to assume that the results for the other dual versus triple component comparisons reflect what would have been observed in an add-on trial.

In summary, while there is only one formal add-on comparison and one exploratory analysis of add-on therapy in non-responders to dual combination therapy, the totality of data consistently demonstrates that subjects receiving the triple combination of various

doses of OM/AML/HCTZ have clinically relevant, better antihypertensive outcomes than subjects on the respective dual combination therapies (Table 9, below).

Table 9. Summary of Major Endpoints for each Dual versus Triple Therapy Comparison

Study Number	Dual Therapy	Triple Therapy	sDBP	sSBP	BP Goal
CS8635-A-E302 (parallel group)	OM/AML 20/5 mg	OM/AML/HCTZ 20/5/12.5 mg	ü ü	ü ü	ü ü
	OM/AML 40/5 mg	OM/AML 40/5/12.5 mg	ü ü	ü ü	ü
		OM/AML 40/5/25 mg	ü ü	ü ü	ü ü
	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/12.5 mg	ü ü	ü ü	ü
		OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü
CS8635-A-E303 (in non-responders)	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/12.5 mg	ü	ü	ü
		OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü ü
CS8635-A-U301 (parallel group)	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü ü
	OM/HCTZ 40/25 mg		ü ü	ü ü	ü ü
	AML/HCTZ 10/25 mg		ü ü	ü ü	ü ü
CS8635-A-U301 (exploratory analysis in non-responders)	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/25 mg	ü	ü	ü
	OM/HCTZ 40/25 mg		ü	ü	ü
	AML/HCTZ 10/25 mg		ü	ü	ü

ü ü = statistically significant benefit of triple versus dual therapy; ü = numerical benefit of triple versus dual therapy.

Supplementary clinical safety data

Studies provided evaluable, supplementary safety data:

Safety data were provided in the pivotal efficacy Studies CS8635-A-E302 and CS8635-A-E303.

Patient exposure

Study CS8635-A-E302

Mean exposure to each dosing regimen for the Safety sets were as follows:

Period I (Safety set 1): 14.1 to 14.2 days (and placebo 14.5 days)

Period II (Primary Safety set): 54.1 to 55.6 days

Period III (Analysis set): 55.3 days

Period IV (Safety set 2): 27.6 to 27.9 days

Period V (Safety set 3): 28.3 to 28.6 days (titration period for responders / non-responders)

Period VI (open label Analysis set): 108.4 days to 205.6 days.

Study CS8635-A-E303

Period I (Safety set 1): 56.6 days

Period II (Safety set 2): 55.8 to 56.0 days

Period III (Period III Analysis set): 55.9 days

Period IV (Safety set 3): 56.5 to 56.8 days

Evaluator's overall conclusions on supplementary clinical safety data

In both studies, the triple combination therapies were well tolerated and the incidence of AEs was low in all treatment groups. No new safety concerns were identified for the triple combination OM/AML/HCTZ therapies or the component dual combination OM/AML therapies. The types of TEAEs observed with the triple combination therapies were similar to those seen with the component dual combination therapies, with no clinically meaningful differences in any of the safety parameters between the triple and dual combination therapies. In Study CS8635-A-E302, a higher incidence of drug-related peripheral oedema was observed in the triple combination and component dual combination treatment groups which included AML 10 mg as a component compared with the groups with the AML 5 mg dose.

Among the subgroups evaluated (age, gender, hypertension severity, and diabetic status), there were slight differences in safety observed between some of the subgroups, however these did not appear to be clinically important. Overall, the safety profiles of the triple combination therapies in both studies were consistent with the safety profiles for the component therapies.

Supplementary round benefit-risk assessment

Supplementary round assessment of benefits

Study CS-8635-A-303 demonstrated that in non-responders to dual therapy OM/AML 40/10 mg, the addition of HCTZ 12.5 or 25 mg provides an additional clinically relevant diastolic and systolic BP lowering effect whether measured by conventional or 24 h ABPM. These data were supported by the demonstration of greater reductions in diastolic and systolic BP in subjects receiving triple-combination therapy compared to the corresponding dual-combinations in the parallel group Study CS-8635-A-302.

Study CS8635-A-U301 (evaluated in the original submission) also demonstrated greater reductions in diastolic and systolic BP in subjects receiving triple-combination therapy (OM/AML/HCTZ 40/10/25 mg) compared to the dual-combinations of OM/AML 40/10 mg, OM/HCTZ 40/25 mg, or AML/HCTZ 10/25 mg. This result was also seen in an exploratory analysis of those subjects who were non-responders to the dual therapies at Week 4, with results for the OM/AML versus OM/AML/HCTZ comparison being consistent with those from Study CS8635-A-E303. It therefore seems not unreasonable to assume that the results for the other comparisons reflect what would have been observed in an add-on trial.

While the studies did not explore add-on therapy for every dose combination for the dual combination therapies, the EMA has previously stated that "If the benefit of add-on therapy is demonstrated using the highest doses of the baseline 2-drug therapy, then it can

be assumed that benefit would also result from addition of the third component to lower doses of the 2-drug combinations."

Supplementary round assessment of risks

The safety profiles of the triple-combination and dual-combination therapies in both studies provided as supplementary data were consistent with the safety profiles for the component therapies, and with those evaluated for the same dose combinations in the original submission.

Supplementary round assessment of benefit-risk balance

On the basis of positive clinical efficacy data and a similar safety profile to the combined individual component therapies, the benefit-risk balance of the triple combination of OM/AML/HCTZ is favourable for add-on therapy in the treatment of hypertension.

Supplementary round recommendation regarding authorisation

The evaluator recommends approval of the submission for Sevikar HCT, subject to modification of the PI.[12]

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the following fixed dose combination tablets:

- Sevikar HCT 20/5/12.5: Olmesartan medoxomil 20 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 12.5mg
- Sevikar HCT 40/10/25 Olmesartan medoxomil 40 mg, amlodipine (as besilate) 10 mg and hydrochlorothiazide 25 mg
- Sevikar HCT 40/10/12.5 Olmesartan medoxomil 40 mg, amlodipine (as besilate) 10 mg and hydrochlorothiazide 12.5mg
- Sevikar HCT 40/5/12.5 Olmesartan medoxomil 40 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 12.5 mg
- Sevikar HCT 40/5/25 Olmesartan medoxomil 40 mg, amlodipine (as besilate) 5 mg and hydrochlorothiazide 25 mg

indicated for:

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

Specific conditions of registration applying to these goods

Notwithstanding that the TGA has granted this application a waiver from the need to submit a Risk Management Plan (RMP), it remains a requirement that Routine Pharmacovigilance of this therapeutic good must be undertaken. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

[12] Details of recommended revisions to the PI are beyond the scope of the AusPAR.

Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes".

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Reports

Therapeutic Goods Administration

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