Public Summary Document

Product: Olmesartan medoxomil and amlodipine and hydrochlorothiazide 20/5/15.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, 40/10/25 mg, Sevikar HCT®.
Sponsor: Merck Sharpe & Dohme
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought a Restricted Benefit listing for a fixed dose combination tablet of olmesartan with amlodipine and hydrochlorothiazide for the treatment of hypertension in patients whose blood pressure is not adequately controlled by two of the following: an angiotensin II receptor antagonist (ATRA), a dihydropyridine calcium channel blocker or a diuretic.

2. Background

This is the first time the PBAC has considered the application for listing a fixed dose combination (FDC) product containing olmesartan, amlodipine and hydrochlorothiazide.

3. Registration Status

The PBAC noted the TGA regulatory application was still pending. At the time of consideration by the PBAC in July 2013, the Clinical Evaluation Report, TGA Delegates Overview and the Advisory Committee on Prescription Medicines (ACPM) recommendation were available.

Olmesartan medoxomil, amlodipine and hydrochlorothiazide (Sevikar HCT) was TGA registered on 20 September 2013 for:

"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.

This fixed dose combination is not indicated for initial therapy"

4. Listing Requested and PBAC's View

Restricted Benefit:
Treatment of hypertension.

- Treatment should not be initiated with this fixed-dose combination
- The condition must not be adequately controlled with two of the following: an angiotensin II antagonist, a dihydropyridine calcium channel blocker or a diuretic.

In addition to prescribing by Medical Practitioners, prescribing as continuing therapy by Nurse Practitioners was requested.

The PBAC considered that the restriction was appropriate as it is consistent with current treatment practice in that patients could switch between different ATRAs, diuretics or dihydropyridine calcium channel blockers.

5. Clinical Place for the Proposed Therapy

The submission proposed that the fixed dose combination product would provide an alternative treatment for hypertension in patients who are not adequately controlled on dual therapy of any two of the individual components of the fixed dose combination or two of other drugs in the same therapeutic classes.

6. Comparator

The submission nominated two comparators:

1. The individual components of Sevikar HCT® (amlodipine, hydrochlorothiazide, olmesartan), either given individually or as combination therapies. The PBAC noted that dual presentations are currently available for amlodipine plus olmesartan, and hydrochlorothiazide plus olmesartan, and amlodipine plus hydrochlorothiazide.
2. Another PBS-listed triple FDC product – Exforge HCT® (amlodipine with hydrochlorothiazide and valsartan).

The PBAC considered these were appropriate comparators

7. Clinical Trials

The submission presented three comparisons using three trials as follows:

1) Clinical study report U301 (also referred to as 'TRINITY') was the primary comparison presented in the submission and is a direct comparison of concomitant administration of olmesartan (O) 40+ amlodipine (AML) 10+ hydrochlorothiazide (HCTZ) 25 vs dual fixed dose components (O40+AML10; O40+HCTZ25; AML10+HCTZ25, all with placebo).

2) Study E105 is a bioequivalence comparison consisting of one open label, 4-period randomised crossover study which examined pharmacokinetic bioequivalence in two patient cohorts:

- A high dose cohort - O40+AML10+HCTZ25 (fixed combination) vs either (O40+AML10)+ HCTZ25, or, (O40+HCTZ25)+AML10;
- A low dose cohort - O20+AML5+HCTZ12.5 (fixed combination) vs either (O20+AML5)+ HCTZ12.5, or, (O20+HCTZ12.5)+AML5

3) An indirect comparison of (O40+AML10+HCTZ25) vs (V320+AML10+HCTZ25) using a randomised controlled trial by Calhoun et al. (2009) which compared valsartan triple therapy fixed dose combination tablets (V320+AML10+HCTZ25) with any dual combination of the components (V320+AML10; V320+HCTZ25; AML10+HCTZ25)), and, using the U301 trial (primary comparison above), via the common reference of the dual treatment arm, AML10+HCTZ25.

Details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Primary comparison		
CSR U301 (also referred to as TRINITY)	A randomized, double-blind, parallel group study evaluating the efficacy and safety of co-administration of a triple combination therapy of olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide in subjects with hypertension.	Clinical Study Report CS8635 - A-U301
Oparil S et al.	Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: The Trinity Multicenter, Randomised, Double-Blind, 12 week Parallel-Group study	*Clin Ther*. (2010); 32: pp.1252-1269
Bioequivalence comparison		
E105	An open label, phase 1, four-period crossover study in healthy subjects to assess the bioequivalence of the highest and lowest dose CS-8635 market image formulations to reference clinical trial formulations and dose proportionality of CS-8635 market image formulations 10 mg amlodipine.	Clinical Study Report CS8635-A-E105
Indirect comparison		
Calhoun et al.	Triple Antihypertensive Therapy with amlodipine, Valsartan, and hydrochlorothiazide: A randomised Clinical Trial.	*Hypertension* (2009); 54: 32-39.

8. Results of Trials

In the U301 trial, triple combination therapy resulted in greater mean reductions from baseline in seated diastolic blood pressure (SeDBP), which were statistically significant, compared to any of the component dual therapies. Similarly, triple combination therapy resulted in greater mean reductions from baseline in seated systolic blood pressure (SeSBP), which were statistically significant, compared to any of the component dual therapies

In Calhoun et al (2009), triple combination therapy resulted in greater SeDBP mean reductions from baseline in SeDBP, which were statistically significant, compared to any of the component dual therapies.

In the indirect comparison between Sevikar HCT® and Exforge HCT®, changes from baseline for systolic and diastolic blood pressure in the common comparator arms were slightly different.

As noted in the submission, there were several significant differences in the design of the trials, particularly duration. The PBAC considered that it was reasonable to accept non-inferiority of the two fixed dose combinations.

The results of the various comparisons are summarised in the tables below:

Mean Seated Diastolic Blood Pressure (mmHg)

	Change from baseline LS Mean (SE)	**Between treatment comparisons LS Mean (95% CI)**
Trial U301		
Sevikar HCT		
AML10/HCTZ25/O40 (n=614)	-21.8 (0.45)	
DUAL THERAPY		**SEVIKAR HCT vs DUAL**
AML10/O40 (n=624)	-18.0 (0.45)	-3.80 (-4.84, -2.76)
HCTZ25/O40 (n=627)	-16.9 (0.45)	-4.90 (-5.94, -3.86)
AML10/HCTZ25 (n=593)[α]	-15.1 (0.46)	-6.70 (-7.76, -5.64)
Calhoun et al 2009		
Exforge HCT		
AML10/HCTZ25/V320 (n=571)	-24.7	
DUAL THERAPY		**EXFORGE HCT vs DUAL**
AML10/HCTZ25 (n=554)[α]	-19.5	-5.3 (-6.36, -4.24)
INDIRECT COMPARISON of Sevikar HCT and Exforge HCT via dual therapy with AML10/HCTZ25		-1.40 (-2.90, 0.10)[β]

AML = amlodipine; CI = confidence interval; HCTZ = hydrochlorothiazide; LS = least squares; O = olmesartan; SE = standard error; V = valsartan

Values in italics were calculated during the evaluation.

[α] Common reference arm for indirect comparison between SEVIKAR HCT and EXFORGE HCT.

[β]In submission, noted as -1.4 (0.065, 2.735). The CI range provided is not plausible and thus was recalculated during the evaluation.

Mean Seated Systolic Blood Pressure (mmHg)

	Change from baseline LS Mean (SE)	Between treatment comparisons LS Mean (95% CI)
Trial U301		
Sevikar HCT		
AML10/HCTZ25/O40 (n=614)	-37.1 (0.74)	
DUAL THERAPY		**SEVIKAR HCT vs DUAL**
AML10/O40 (n=624)	-30.0 (0.74)	-7.1 (-8.81, -5.39)
HCTZ25/O40 (n=627)	-29.7 (0.73)	-7.4 (-9.09, -5.71)
AML10/HCTZ25 (n=593)[α]	-27.5 (0.76)	-9.6 (-11.33, -7.87)
Calhoun et al 2009		
Exforge HCT		
AML10/HCTZ25/V320 (n=571)	-39.7	
DUAL THERAPY		**EXFORGE HCT vs DUAL**
AML10/HCTZ25 (n=554)[α]	-31.5	-8.2 (-9.87, -6.53)
INDIRECT COMPARISON of Sevikar HCT and Exforge HCT via dual therapy with AML10/HCTZ25		-1.40 (-3.80, 1.00)[§]

AML = amlodipine; CI = confidence interval; HCTZ = hydrochlorothiazide; O = olmesartan; SE = standard error; V = valsartan.
Values in italics were calculated during the evaluation.
[α] Common reference arm for indirect comparison between Sevikar HCT and Exforge HCT.
[§] In Submission, noted as -1.40 (-3.61, 0.81). Recalculated during evaluation.

The PBAC noted that bioequivalence data for the comparison of Sevikar HCT with its components were presented in the submission.

With regard to comparative harms, the components of Sevikar HCT have well-established safety profiles. The PBAC agreed with the ESC that it was reasonable to consider that there were no substantial differences in safety between the high dose of the fixed triple combination and corresponding high doses of the dual combination components in trial U301. The incidence of hypotension in the trial was low, although the clinical study report stated hypotension was higher in the AML10/HCTZ25/O40 treatment arm (2.1%) compared to the other treatment arms (0.0% to 0.7%). Patients with uncontrolled type 1 or 2 diabetes mellitus were excluded from the trial.–Participants in U301 were likely to be younger and healthier (less co-morbidity) than the proposed Australian population.

No formal indirect comparison of safety was presented between Sevikar HCT and Exforge HCT in the submission. The PBAC noted that the formulations presented in the submission allow for olmesartan to be up titrated before amlodipine or hydrochlorothiazide. This is different to the presentations of Exforge HCT. Only one formulation of Sevikar HCT contains the lower 20 mg dose of olmesartan, while the remaining four formulations have the higher dose of olmesartan 40 mg.

The PBAC expressed concern about the trade names of fixed dose combinations which do not make the three components clear for prescribers.

The most recent safety update report for olmesartan does not suggest any new safety signals.

9. Clinical Claim

The submission described Sevikar HCT fixed-dose combination as:

- Superior in terms of comparative effectiveness compared to the individual components given as dual therapy, and, equivalent to the sum of the components given concomitantly. These claims were supported by study U301 and by bioequivalence data;
- Similar in terms of safety and tolerability versus the components at corresponding doses;
- Non-inferior to AML10+HCTZ25+V320. This claim was based on an indirect comparison of two trials. There were exchangeability issues between the trials and the calculated least square mean for both seated diastolic and seated systolic blood pressure outcomes were noted by the PBAC to be wide.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the claim that Sevikar HCT is non-inferior to its individual components given concomitantly.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net financial saving/year for the R/PBS of less than $10 million in Year 5. The financial implications are to be further verified.

The PBAC agreed that it is difficult to predict the extent of replacement of different strengths of Exforge HCT by Sevikar HCT and that this assumed replacement will determine any savings. The PBAC considered that the addition of an alternative triple combination for treatment of hypertension may expand the use of these products but is unlikely to increase the total market for hypertensive products overall. The PBAC noted that the impact of an alternative triple combination may lead to prescribers choosing valsartan or olmesartan in place of a cheaper angiotensin converting enzyme inhibitors products and this would negate the proposed savings.

Overall the PBAC accepted that there may be small financial savings following the listing of Sevikar HCT and that at worst, the listing would be cost-neutral.

12. Recommendation and Reasons

The PBAC recommended listing of olmesartan medoxomil and amlodipine and hydrochlorothiazide 20/5/15.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, 40/10/25 mg (Sevikar HCT®) as a Restricted benefit for treatment of hypertension in a patient who meets certain criteria, on a cost minimisation basis compared to the individual components given concomitantly.

The PBAC accepted the claim of non-inferiority of Sevikar HCT compared to Exforge HCT and the claim of superiority to formulations containing any two of the three components of

Sevikar HCT (amlodipine, hydrochlorothiazide and olmesartan). The PBAC accepted the claim of similar safety and tolerability compared to the components.

The PBAC accepted that the listing might result in a small financial save to Government and agreed that in the worst case, the listing should be cost-neutral.

The PBAC noted that there are some quality use of medicines issues associated with the large number of fixed dose combination products listed on the PBS for treatment of hypertension; these include lack of clarity regarding the type and number of ingredients because of brand names, different titration patterns provided by each brand, and potential for consumer and prescriber confusion.

The PBAC recommended that all proposed strengths of Sevikar HCT are suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

Outcome:
Recommended

Recommended Listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
AMLODIPINE + HYDROCHLOROTHIAZIDE + OLMESARTAN MEDOXOMIL			
amlodipine 5 mg + hydrochlorothiazide 12.5 mg + olmesartan medoxomil 20 mg tablet, 30	30	5	Sevikar HCT MK 20/5/12.5
amlodipine 5 mg + hydrochlorothiazide 12.5 mg + olmesartan medoxomil 40 mg tablet, 30	30	5	Sevikar HCT MK 40/5/12.5
amlodipine 5 mg + hydrochlorothiazide 25 mg + olmesartan medoxomil 40 mg tablet, 30	30	5	Sevikar HCT MK 40/5/25
amlodipine 10 mg + hydrochlorothiazide 12.5 mg + olmesartan medoxomil 40 mg tablet, 30	30	5	Sevikar HCT MK 40/10/12.5
amlodipine 10 mg + hydrochlorothiazide 25 mg + olmesartan medoxomil 40 mg tablet, 30	30	5	Sevikar HCT MK 40/10/25

Condition/Indication:	Hypertension
Restriction:	Restricted benefit
Clinical criteria:	Treatment must not be initiated with this fixed-dose combination AND The condition must not be adequately controlled with two of the following: an angiotensin II antagonist, a dihydropyridine calcium channel blocker or a diuretic.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.