PUBLIC SUMMARY DOCUMENT
Product: AMLODIPINE (as besylate) with VALSARTAN and HYDROCHLOROTHIAZIDE, tablets, 5 mg-160 mg-12.5 mg, 5 mg-160 mg-25 mg, 10 mg-160 mg-12.5 mg, 10 mg-160 mg-25 mg, and 10 mg-320 mg-25 mg, Exforge HCT®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

To request a Restricted Benefit listing for a fixed dose combination tablet of amlodipine with valsartan and hydrochlorothiazide (HCTZ) for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine and valsartan and HCTZ, taken either as individual or combination therapies.

2. Background

The fixed dose combination item containing amlodipine with valsartan and HCTZ had not previously been considered by the PBAC.

3. Registration Status

All the five strengths of amlodipine with valsartan and HCTZ fixed dose combination tablets were TGA registered on 9 April 2010 for use only as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations.

4. Listing Requested and PBAC's View

Restricted Benefit

Hypertension in patients already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide (as individual or combination therapies).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Many patients with hypertension require three or more agents to achieve target blood pressure. Combining three antihypertensive compounds with complimentary mechanisms to control blood pressure in a single tablet formulation reduces the tablet burden.

6. Comparator

The submission nominated the three component products - amlodipine, valsartan and HCTZ given concomitantly as the main comparator.

7. Clinical Trials

The submission presented two direct, randomised, open-label, cross-over bioequivalence trials (2305 and 2306), to determine the relative bioavailability of 5/160/12.5 mg and 10/160/25 mg combinations compared to their free forms (three components taken concomitantly) and one randomised double-blind, parallel-group trial (2302) to evaluate the additive efficacy and safety of triple fixed dose combination of Exforge HCT® compared

with all three possible dual components (amlodipine/valsartan; HCT/valsartan and amlodipine/HCT).

The key trial published at the time of submission is shown in the table below:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Non-direct randomised trial: Triple vs. dual - additive effectiveness and safety		
VEA489A2302 (*referred to as Study 2302*) Calhoun, D.A. et al (2009)	Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: A randomized clinical trial.	Hypertension 2009; 54 (1):pp32-9

8. Results of Trials

Effectiveness – bioequivalence studies

The bioequivalence studies, 2305 and 2306, compared relevant treatment arms. The endpoints examined in these studies were pharmacokinetic parameters to demonstrate bioequivalence between the fixed and free forms of the three components.

The acceptance range for bioequivalence, used in the submission, was that the 90% confidence interval for the ratio of geometric means should lie within 0.80 to 1.25. The 80-125% range is accepted on the basis that for most 'uncomplicated' drugs, a -20% to +25% variation in plasma concentrations would not be considered clinically important.

Overall, the rates (Cmax) and extent of absorption (AUC) of amlodipine, valsartan and HCT, were similar between the fixed and free combinations for both strengths (5/160/12.5 mg and 10/160/25 mg) of the triple fixed dose combination. The results indicate that for Study 2305, the 90% confidence intervals for the ratios of geometric means for AUC_{0-t}, $AUC_{0-\infty}$ and Cmax for valsartan, amlodipine and HCT (5/160/12.5 mg) were within the required bioequivalence range of 0.8-1.25. This suggests that the rate and extent of absorption for the three fixed component treatment was similar to that of the free combination treatment. The results were similar for Study 2306 which examined the bioequivalence of the 10/160/25 mg strength of the fixed dose combination with the free combination treatment.

Effectiveness – additive effectiveness of triple fixed combination compared to dual fixed combination: Study 2302.

The results from Study 2302 provided evidence on additive effectiveness of Exforge HCT® (that is, where Exforge is used as an add-on of a third component to a dual combination therapy). The ESC advised that the results of this study should be interpreted with caution given the limited external validity of the trial population.

The within treatment analysis of the primary endpoints demonstrated that there were statistically significant reductions from baseline in mean sitting diastolic blood pressure (MSDBP) and mean sitting systolic blood pressure (MSSBP) for all 4 treatment arms at endpoint (Week 9). The greatest reductions in BP were observed with triple therapy. The between-treatment comparison demonstrated that triple therapy was clinically and statistically superior to all three dual therapies in reducing both diastolic and systolic blood pressure at endpoint in the ITT population. Results of the between-treatment comparisons at

Weeks 5, 7 and 9 were similar to those observed at endpoint for the intent-to-treat (ITT) patients. Similar results at endpoint were also obtained for the per protocol population.

Exforge HCT® was superior to dual combination therapy for the majority of secondary endpoints, which included blood pressure (BP) control rates.

In the bioequivalence studies (2305 & 2306), both fixed and free combinations appeared to be well tolerated at the administered dosages. Neither study reported serious adverse events/deaths nor clinically important changes in vital signs/clinical laboratory measurements.

In Study 2302, the most frequently observed adverse events in the triple therapy arm were dizziness and peripheral oedema. No details of other types of oedema were presented in the submission. Of these two types of events, dizziness was more frequent in the triple therapy arm compared to all dual therapy arms. The incidence of dizziness was comparable between triple therapy (7.7%) and valsartan/HCT (7.0%) but occurred less frequently with valsartan/amlodipine (2.3%) and HCT/amlodipine (3.9%).

9. Clinical Claim

The submission described Exforge HCT® as superior to the dual combinations of its components and as bioequivalent to the three individual components taken concomitantly. The PBAC accepted this claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were determined in the submission as follows:

- Exforge HCT® 5/160/12.5mg once daily (QD) was equivalent to the concomitant use of Exforge (amlodipine/valsartan) 5/160mg and HCT 12.5mg (once daily);
- Exforge HCT® 5/160/25mg QD was equivalent to the concomitant use of Exforge (amlodipine/valsartan) 5/160mg and HCT 25mg (once daily);
- Exforge HCT® 10/160/12.5mg QD was equivalent to the concomitant use of Exforge (amlodipine/valsartan) 10/160mg and HCT 12.5mg (once daily);
- Exforge HCT® 10/160/25mg QD was equivalent to the concomitant use of Exforge (amlodipine/valsartan) 10/160mg and HCT 25mg (once daily); and
- Exforge HCT® 10/320/25mg QD was equivalent to the concomitant use of Exforge (amlodipine/valsartan) 10/320mg and HCT 25mg or Co-Diovan® (valsartan-HCT) 320/25mg and amlodipine 10mg (once daily).

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated to be between 10,000 and 50,000 in Year 5.

The financial savings per year to the PBS were estimated to be less than $10 million per year in Year 5. The submission's estimate was based on Exforge HCT® being restricted to patients stabilised on its three components given as triple therapy, as per the requested restriction presented in the submission. This is different to the restriction recommended by PBAC.

12. Recommendation and Reasons

The PBAC recommended listing of amlodipine with valsartan and hydrochlorothiazide on the PBS as a Restricted Benefit listing for hypertension in a patient who is not adequately controlled with any two of the drugs in the combination in accordance with the combination guidelines, on a cost-minimisation basis compared with the constituent components at equivalent doses.

The PBAC noted that the listing would allow add-on as well as substitution therapy but considered that this was consistent with current guidelines and clinical practice for the treatment of hypertension. It is also consistent with recommendations made by the PBAC at the March 2010 meeting regarding the ACEI/ATRA with diuretic combination products and the ACEI/ATRA with calcium channel blocker and is a pragmatic approach

The PBAC noted that although most of the data provided were for bioequivalence (Study 2305 and 2306), it accepted that the triple combination was superior to all three dual combinations of its components in reducing blood pressure (Study 2302) and bioequivalent to the three individual components taken concomitantly. The observed safety profile was consistent with the known pharmacological effects of an angiotensin II receptor blocker, a thiazide diuretic and a calcium channel blocker.

The PBAC decided it was not satisfied as required by section 101 (4AC) of the *National Health Act 1953* and therefore it will not provide advice to the Minister under that subsection in relation to the following combination item: amlodipine (as besylate) with valsartan and hydrochlorothiazide, tablets, 5 mg-160 mg-12.5 mg, 5 mg-160 mg-25 mg, 10 mg-160 mg-12.5 mg, 10 mg-160 mg-25 mg, and 10 mg-320 mg-25 mg which have the brand name Exforge HCT. The PBAC noted that there was no basis to conclude that any of these combination products have any significant improvement in compliance, efficacy or reduction in toxicity over their alternative therapies for some patients.

Recommendation:

AMLODIPINE (as besylate) with VALSARTAN and HYDROCHLOROTHIAZIDE, tablets, 5 mg-160 mg-12.5 mg, 5 mg-160 mg-25 mg, 10 mg-160 mg-12.5 mg, 10 mg-160 mg-25 mg, and 10 mg-320 mg-25 mg, Exforge HCT®

Restriction:	Restricted Benefit Hypertension in a patient who is not adequately controlled with any two of the drugs in the combination.
Maximum quantity:	28
Repeats:	5

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

Novartis Pharmaceuticals Australia welcomes the PBAC's recommendation to make Exforge HCT® available to patients with hypertension, which is not adequately controlled with two of the drugs in the combination.