PUBLIC SUMMARY DOCUMENT
Product: TRANDOLAPRIL with VERAPAMIL HYDROCHLORIDE, tablet, 2 mg-180 mg, 4 mg-240 mg, Tarka®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application
The submission sought listing for a combination tablet of trandolapril with verapamil as a restricted benefit for "the treatment of hypertension. Treatment should not be initiated with this fixed dose combination."

2. Background
This combination formulation has not previously been considered by the PBAC.

3. Registration Status
Trandolapril with verapamil hydrochloride was registered by the TGA on 24 October 2005 and is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

4. Listing Requested and PBAC's View
Restricted benefit
The treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy
The use of Tarka would require the administration of a single tablet daily as opposed to one tablet of each monotherapy agent daily.

6. Comparator
The submission nominated trandolapril and verapamil Slow Release (SR) used concomitantly; and also used individually in order to demonstrate an additional effect as the comparators.

See Recommendations and Reasons for the PBAC's view.

7. Clinical Trials
The submission presented five key trials that compared the short-term efficacy and safety of Tarka with either trandolapril and/or verapamil SR monotherapy in the treatment of hypertension. Four of 5 trials (MPF/H9507, MPF/H9510, VT067 and MPF/H9508) were randomised, double-blind, parallel-group trials. Of those four, one (MPF/H9508) was inappropriately included as a key trial due to the use of non-comparable doses. One of 5 trials (Karlberg et al, 2000) was a randomised, double-blind, cross-over trial. A meta-analysis was presented pooling the results of 3 trials (MPF/H9507, MPF/H9510 and VT067).

In addition, 6 studies were included as supporting evidence. Five of the 6 studies were randomised, double-blind, parallel-group trials comparing the short-term efficacy and safety of Tarka with either trandolapril or/and verapamil SR monotherapy in the treatment of

hypertension. Four of those evaluate doses that were different from the requested strengths for listing, and one (Ruilope et al, 1999) was conducted in a diabetic population.

The full list of trials forming the basis of the submission is tabulated below.

Trial/First author	Protocol title	Publication citation
Karlberg BE 2000	Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. Swedish TARKA Trialists.	Blood Press 2000;9:140-5.
MPF/H9507 Viskoper RJ 1997	Verapamil and trandolapril alone and in fixed combination in moderate essential hypertension: a multicenter, double-masked study. Verapamil and trandolapril alone and in fixed combination on 24-hour ambulatory blood pressure profiles of patients with moderate essential hypertension.	Current Therapeutic Research 1997;58(6):331-42. Current Therapeutic Research 1997;58(6):343-51.
MPF/H9510	A double-blind, randomised, parallel group study comparing the efficacy and safety of two trandolapril/verapamil SR dose combination with trandolapril monotherapy in essential hypertensive patients who have not responded sufficiently to trandolapril monotherapy.	
VT 067	Antihypertensive efficacy and safety of verapamil SR 180mg/trandolapril 2mg in patients insufficiently pre-treated with single-blind trandolapril 2mg monotherapy. A double-blind randomised parallel-group comparison to trandolapril 2mg.	
MPF/H9508*	Double-blind, placebo-controlled clinical study to determine the influence of trandolapril, VeraTran, and a beta blocker-diuretic combination on the physical performance and pulmonary function in patients with mild to moderate hypertension.	

8. Results of Trials

The results of 4 key trials are summarised in the tables below.

Summary of the primary efficacy result in key trials

Trial	ITT n	Mean change of sitting diastolic BP in mmHg from baseline to last visit (95% CI)	Difference of change in sitting diastolic BP (mmHg) of combination over monotherapy
Karlberg 2000 - VT180/2 - V240 or T2	Total= 197	 -15.1 -12.4 / -10.5	 VT180/2 versus (V240 or T2) = -3.58 (95% CI: -2.40, -4.76)
MPF/H9507 - VT180/2 - V180 - T2	 103 102 105	 -13.4 (-14.9, -11.9) -9.8 (-11.4, -8.3) -11.3 (-13.1, -9.4)	 VT180/2 versus V180 = -3.6 (p=0.0005) VT180/2 versus T2 = -2.3 (p=0.017)
MPF/H9510 - VT180/1 - VT180/2 - T2	 69 75 74	 -7.15 -9.36 -7.54	 V180/2 versus T2 = -1.8 (p=0.076)
VT067 - VT180/2 - T2	 184 185	 -7.0 (-8.2, -5.8) -3.5 (-4.7, -2.4)	 V180/2 versus T2 = -3.7 (p<0.001)

VT180/2 = verapamil SR 180mg/trandolapril 2mg; VT180/1 = verapamil SR 180mg/trandolapril 1mg; V240 = verapamil SR 240mg; V180 = verapamil SR 180mg; T2 = trandolapril 2mg; ITT = intention-to-treat; BP = blood pressure

Summary of response rates * (VT180/2 versus T2) of 3 key rials included in the meta-analysis

ITT population	Point estimate	95% CI	p-value	Heterogeneity
Relative risk (combined)				Chi^2=9.74
Fixed effect model	1.44	1.22 to 1.69	<0.0001	p=0.008
Random effects model	*1.40*	*0.97 to 2.01*	*0.07*	
Risk difference (combined)				Chi^2=4.21
Fixed effect model	0.16	0.09 to 0.23	<0.0001	p=0.12
Random effects model	0.15	0.04 to 0.25	<0.006	

* defined as a reduction in diastolic blood pressure of >10mmHg or diastolic blood pressure <90mmHg
VT180/2 = verapamil SR 180mg/trandolapril 2mg; T2 = trandolapril 2mg; ITT = intention-to-treat;

The primary outcome of 4 key trials was change in sitting diastolic BP from baseline to the last visit.

Three of five trials (MPF/H9570, MPF/H9510 and VT067) compared the reduction in diastolic BP of Ziaxel® 180/2mg with trandolapril 2mg monotherapy. The results showed the contribution of verapamil SR 180mg to diastolic BP reduction ranged from -1.8 to -3.7mmHg.

The results of the meta-analysis for risk difference showed a response rate of 0.16 (95% CI: 0.09 to 0.23; p<0.0001) that was significantly higher for the combination therapy. However, based on the relative risk, the result failed to reach statistical significance: RR=1.41(95% CI: 0.98 to 2.02; p=0.0635).

Tarka had a similar adverse effect profile to that of trandolapril and verapamil SR, with the most common adverse effects being cough, headache and constipation. The rate of adverse events seemed to be similar between the fixed-dose combination and either trandolapril or verapamil SR monotherapy in all trials. An exception was the Ruilope et al, 2004 supporting trial, in which, the rate of adverse events was about twice as likely in the verapamil SR/trandolapril 180/2mg arm compared with the trandolapril 2mg arm (RR=0.46; 95% CI: 0.25-0.84; p=0.010).

See Recommendations and Reasons for the PBAC's view.

9. Clinical Claim

The submission described Tarka (2/180mg and 4/240mg) as having significant advantages in effectiveness over verapamil SR or trandolapril given as individual therapy.

The PBAC agreed the claim of superiority of the combinations of trandolapril and verapamil over either individual agenda as monotherapy was weakly supported by the data.

10. Economic Analysis

The submission presented a preliminary (trial-based) economic evaluation adopting a cost-minimisation approach. The resources included were drug costs only.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 3 of listing the financial cost would be less than $10 million per year .
The PBAC considered that this was an overestimate.

12. Recommendation and Reasons

The PBAC considered that verapamil is not a drug of choice in the treatment of hypertension and treatment of angina would constitute the majority of its use. Further, it was the view of the PBAC that it is possible that the combination could be used in patients with both hypertension and angina, which is beyond the requested restriction and no evidence is provided to demonstrate an additive effect across these two indications. There is also the potential that the proposed combination drug product could replace ACE inhibitor with thiazide combinations, which are less costly than the proposed combination presentations and there is no evidence of comparative effectiveness against these combinations. Further, in either of the above situations, the financial implications would have been underestimated. The PBAC considered that it was doubtful whether this combination meets the criteria for listing combination products in terms encouraging inappropriate increase in utilisation of the components.

Data presented in the submission indicate that approximately 400 patients in Australia are on concomitant trandolapril and verapamil therapy and it is not known how many of these are being treated for hypertension in the absence of angina. Thus, the PBAC was of the view that the clinical need for this combination product was not clearly demonstrated.

The PBAC agreed the claim of superiority of the combination of trandolapril and verapamil SR over either individual component as monotherapy in lowering blood pressure was weakly supported by the data. One of five trials (MPF/H9507) compared the reduction in diastolic blood pressure (BP) of Ziaxel® 180/2 mg with verapamil 180 mg monotherapy and reported a statistically significant further reduction of -3.6 mmHg. Three of five trials (MPF/H9507, MPF/H9510 and VT067) compared the reduction in diastolic BP of Ziaxel® 180/2 mg with trandolapril 2 mg monotherapy. These results show the addition of verapamil SR 180 mg to trandolapril in terms of diastolic BP reduction is less convincing, varying from -1.8 mmHg to -3.7 mmHg, which when pooled (random effects) is -2.80 mmHg (95% CI: -3.99 mmHg to -1.60 mmHg). An excluded fourth randomised trial also comparing the 180/2 combination with trandolapril 2 mg monotherapy reported a non-statistically significant difference of -1.3 mmHg, but this small trial is unlikely to have a substantial impact when included in the meta-analysis. According to the Committee for Proprietary Medicinal Products (CPMP) guidelines, a 2 mmHg margin is considered the minimum clinically acceptable difference in diastolic BP (DBP). The PBAC also noted that only data corresponding to the lower dose combination was provided. The PBAC was thus not entirely convinced that this combination meets its criteria for listing combination products in terms of demonstrating superiority of the combination over both of its individual components.

Further, the PBAC also noted that a review (Prospective Studies Collaboration) has suggested that systolic blood pressure (SBP) is a more useful predictor of subsequent clinical outcomes than DBP. The PBAC noted that inspection of the SBP results suggested greater numerical differences would likely be generated if these results were similarly pooled to the results for DBP and this was confirmed by the sponsor's pre-PBAC Response.

The PBAC therefore rejected the submission because of a lack of clinical need in patients with hypertension for the combination, concerns about inappropriate substitution for ACE inhibitor with thiazide combinations and unconvincing evidence of superiority over the individual components in the requested doses.

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 believes that there is a clear clinical need for a combination of trandolapril and verapamil. Although the submission provided data that there are currently over 23,000 Australians receiving an ACE inhibitor/ calcium channel blocker combination, the PBAC focused on the smaller number currently on the verapamil/ trandolapril combination when assessing clinical need.

In addition, arguments that at a population level there is a limited need for the product do not appear to take into account the fact that for individual patients the combination of trandolapril and verapamil may provide substantial benefit in controlling hypertension. The National Heart Foundation guidelines "Hypertension Management Guide for Doctors 2004" indicates that a combination ACE inhibitor and Calcium channel Blocker is useful and has a "particular role in the presence of diabetes and lipid abnormalities" (see Page 21). The sponsor would like to work with the PBAC to examine future listing options.