PUBLIC SUMMARY DOCUMENT

Product: Trandolapril with Verapamil Hydrochloride-SR, film-coated tablet, 4 mg – 240 mg (sustained release), Tarka®

Sponsor: Abbott Australasia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission requested a restricted benefit listing for the treatment of hypertension (high blood pressure) in patients who are not adequately controlled with 4 mg of trandolapril monotherapy.

2. Background

At the November 2005 meeting, the PBAC rejected a submission for a restricted benefit listing for trandolapril with verapamil (Tarka) for the treatment of hypertension because of a lack of clinical need in patients with hypertension for the combination, concerns about inappropriate substitution for angiotensin converting enzyme (ACE) + thiazide combinations and unconvincing evidence of superiority over the individual components in the requested doses.

3. Registration Status

Tarka was registered by the TGA on 20 October 2004 for "the treatment of hypertension. Treatment should not be initiated with this fixed dose combination".

4. Listing Requested and PBAC's View

Restricted benefit
For the treatment of hypertension in patients who are not adequately controlled with 4 mg of trandolapril monotherapy.

5. Clinical Place for the Proposed Therapy

Tarka provides an alternative to thiazide (diuretic) combinations and it is claimed that Tarka provides similar improvements in blood pressure whilst resulting in lower rate of new-onset diabetes.

6. Comparator

The resubmission nominated trandolapril or verapamil-SR given as monotherapy as the main comparators. This is as previously agreed by the PBAC.

7. Clinical Trials

The resubmission presented a new pivotal trial, a randomised controlled trial (TV-51-HTN) comparing Tarka with trandolapril (4 mg) and verapamil (240 mg) monotherapies in patients with mild to moderate essential hypertension.

This trial had been published at the time of resubmission, as follows:

Trial/First author	Protocol title	Publication citation
TV-51		
Messerli et al (1998)	Effects of verapamil and trandolapril in the treatment of hypertension.	Hypertension 11: 322-327.

The Study of Trandolapril/verapamil-SR and Insulin Resistance (STAR) comparing trandolapril/verapamil-SR and losartan/hydrochlorothiazide in patients with metabolic syndrome was provided as supportive evidence, and the bioequivalence study (TV-4-CP) as a reference supporting the bioequivalence between Tarka 4/240 and its individual components of trandolapril 4 mg and verapamil-SR 240 mg given concomitantly.

8. Results of Trials

The pivotal trial (TV-51-HTN) result showed for the primary endpoint of sitting diastolic blood pressure (DBP), that all active treatment groups had statistically significant lower endpoint mean trough sitting DBP compared to placebo ($p<0.01$). At endpoint, the combination therapy of trandolaril/verapamil had a statistically significant lower mean trough sitting DBP compared to its monotherapies ($p<0.01$). The combination provided a further -3.6 mmHg reduction in blood pressure versus trandolapril and a further -3.8 mmHg reduction compared to verapamil-SR.

The results from the STAR trial showed that the 2-hour oral glucose tolerance test (OGTT) adjusted mean change in blood glucose level for patients on trandolapril/verapamil-SR was -3.8 mg/dL compared to +26 mg/dL for patients on losartan/hydrochlorothiazide. This difference was statistically significant ($p<0.001$). Between Weeks 8 and 39, there was significantly better control over the systolic blood pressure in losartan/hydrochlorothiazide group, although differences were not statistically significant at study end.

The combination of trandolapril and verapamil-SR was associated with more reports of chest pain and joint pain compared to the individual components and placebo in the pivotal trial of TV-51-HTN. Significantly more events were observed in patients with the combination therapy of trandolapril and verapamil-SR in cough and pain in the extremity in the STAR trial.

9. Clinical Claim

The resubmission described Tarka as being significantly more effective than the individual components given as monotherapy and was no worse in terms of efficacy and safety than the individual components given concomitantly.

10. Economic Analysis

The resubmission presented an updated preliminary economic evaluation. A treatment course of 28 days was used in the updated evaluation compared to a 30-day course in the previous submission.

11. Estimated PBS Usage and Financial Implications

The resubmission estimated that in Year 3 of listing, the likely number of patients would be in the range 10,000 – 50,000 and the financial net cost to the PBS would be < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis compared with the corresponding strengths of the trandolapril and verapamil hydrochloride sustained release constituents. The PBAC noted that the sponsor had agreed that patients be stabilised on monotherapy with both drugs at the doses contained in the combination, before moving to the combination product.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation
TRANDOLAPRIL with VERAPAMIL HYDROCHLORIDE-SR, film-coated tablet, 4 mg – 240 mg (sustained release)

Restriction: CAUTION:
The myocardial depressant effects of verapamil hydrochloride and of beta-blocking drugs are additive.

Restricted Benefit
Hypertension in a patient who is stabilised on treatment with trandolapril 4 mg and verapamil hydrochloride sustained release 240 mg.

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
The sponsor has no comment.