

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Ramipril with Felodipine, tablets, 2.5 mg-2.5 mg, 5 mg-5 mg Triasyn<sup>®</sup>

**Sponsor:** Sanofi-Aventis Australia Pty Ltd

**Date of PBAC Consideration:** March 2007

### **1. Purpose of Application:**

The submission sought listing for the treatment of hypertension in patients who are not adequately controlled with either ramipril or felodipine monotherapy, or who are receiving ramipril and felodipine concurrently.

### **2. Background:**

This product has not been previously considered by the PBAC.

### **3. Registration Status:**

The product was registered by the TGA on 2 December 1998 for the treatment of mild to moderate hypertension. This combination should not be used to commence therapy.

### **4. Listing requested and PBAC's View**

#### Restricted benefit

For the treatment of hypertension in patients who are not adequately controlled with either ramipril or felodipine monotherapy, or who are receiving ramipril and felodipine concurrently.

*See Recommendation and Reasons for PBAC's view.*

### **5. Clinical place for the proposed therapy:**

Triasyn will be used predominantly by patients who are currently treated with felodipine or ramipril (or both concomitantly) for the treatment of hypertension.

### **6. Comparator:**

The submission nominated ramipril and felodipine extended release (ER) monotherapies as the appropriate comparators.

### **7. Clinical trials:**

The scientific basis of comparison consisted of four randomised head-to-head studies comparing the short-term efficacy and safety of ramipril and felodipine combination therapy to either ramipril or felodipine monotherapy in the treatment of hypertension. A meta-analysis pooling the results of three of these trials was presented.

The following is the list of trials forming the basis of the submission.

## List of trials forming the basis of the submission

Parallel-group trial	
Trial/Author	Title/Source
Study B1 HOE/9869/2/303/HT  Published as: Scholze J et al.	Randomised double-blind multicentre study of the efficacy, tolerability and safety of various combinations of ramipril (HOE 498) and felodipine ER in patients with mild to moderate essential hypertension  Antihypertensive profiles with ascending dose combinations of ramipril and felodipine ER. <i>Clinical &amp; Experimental Hypertension</i> (New York). 21(8):1447-62, 1999 Nov
Study B2 CF -501	Efficacy and tolerability of two fixed combinations of felodipine ER and ramipril in hypertensive patients. An international multicentre study
Study B3 HOE/9869/2/MN/304/HT  Published as: Poisson P et al.	Randomised double-blind study of the efficacy and safety of the fixed combination 2.5mg ramipril/2.5mg felodipine ER (HOE 9869) compared to the components in hypertensive patients  Ramipril and felodipine: a comparison of the efficacy and safety of monotherapy versus combination therapy. <i>Current Medical Research &amp; Opinion</i> . 13(8):445-56, 1996.
Study B4 HOE 498/2/B/302/HT	Randomised double-blind study of the efficacy, safety and tolerability of the combination of 5mg ramipril and 5mg felodipine daily vs. 5mg ramipril daily in subjects suffering from mild to moderate uncomplicated essential hypertension unresponsive to monotherapy with 5mg ramipril daily

## 8. Results of trials

Two of the four trials compared the reduction in diastolic blood pressure (DBP) and systolic blood pressure (SBP) of combination therapy with felodipine 5mg monotherapy. The results in supine DBP showed that the contribution of ramipril 5mg varied from -2.3 to -2.7mmHg. The mean differences in reduction of supine SBP were larger and ranged from -2.8 to -9.5mmHg.

Three of the trials compared the additive effect of felodipine 5mg. The reductions of supine DBP varied from -3.2 to -5.8mmHg, greater than the clinically important margin of 2mmHg. The reductions in supine SBP ranged from -4.8 to -9.5mmHg. The results suggested that the addition of felodipine 5mg to ramipril 5mg produced a greater reduction in DBP than the addition of ramipril 5mg to felodipine 5mg, which was also supported by the results of the meta-analysis.

For the comparisons between felodipine/ramipril 2.5/2.5 mg versus either felodipine or ramipril monotherapy in doses of 2.5 mg and 5 mg, the mean change in supine DBP ranged from -1.09 to - 2.1mmHg. The reductions of SBP of the combination (felodipine/ramipril 2.5/2.5 mg) over felodipine 2.5 mg or ramipril 2.5 mg were -4.3mmHg and -3.3mmHg respectively and were statistically significant.

Triasyn had similar side effects to the individual components, ramipril and felodipine. The common side effects were headache, dry cough, dizziness, and hot flushes.

## **9. Clinical Claim**

On the basis of the results presented, and because a cost-minimisation approach was most appropriate for this combination product, the category that best described the proposed drug is that the drug is considered to be no worse than the main comparator in terms of effectiveness and toxicity.

*See Recommendations and Reasons for PBAC's view*

## **10. Economic analysis**

The preliminary economic evaluation presented adopted a cost minimisation approach. The resources included were drug costs only.

## **11. Estimated PBS Usage and Financial Implications:**

The number of patients was estimated to be < 10,000 in Year 4.

The submission estimated that the financial impact to government is likely to be modest savings of less than \$45,000 per year.

## **12. Recommendation and Reasons:**

The PBAC recommended listing on a cost-minimisation basis compared with the corresponding strengths of the ramipril and felodipine components given concomitantly.

The PBAC expressed concern that the combination product does not provide all the dose possibilities afforded by the single agent products, with ramipril available in four, and felodipine available in three strengths, respectively. While this was expected to make dose titration more difficult in the clinical setting, it did not constitute a reason for rejection.

### ***Recommendation***

RAMIPRIL with FELODIPINE, tablets, 2.5 mg-2.5 mg, 5 mg-5 mg

Restriction:                      Restricted benefit  
Hypertension in a patient not adequately controlled with either ramipril or felodipine monotherapy.

Maximum quantity: 30

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**

Sanofi-aventis welcomes the PBAC's positive recommendation of Triasyn. Sanofi-aventis feels that Triasyn will be a useful addition in the treatment of hypertension.