PUBLIC SUMMARY DOCUMENT

Product: Sevelamer hydrochloride, tablet, 800 mg, Renagel®

Sponsor: Genzyme Australasia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought an authority required listing for the treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis.

2. Background

At the March 2006 meeting, the PBAC rejected a submission for a restricted benefit listing for the treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products because of a lack of convincing evidence of increased efficacy or safety overall, and a high and uncertain cost-effectiveness. *(See also Public Summary Document for March 2006).*

At the November 2006 meeting, the PBAC rejected a re-submission for an authority required listing for the treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis because of uncertain clinical benefit and uncertain cost-effectiveness. *(See also Public Summary Document for November 2006).*

3. Registration Status

Sevelamer was registered on 28 June 2005 for the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease.

4. Listing Requested and PBAC's View

Four PBS listings were proposed. These varied in whether or not they included age limits, indicators of disease severity or other restrictions on PBS use.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Sevelamer provides an alternative to calcium-based phosphate binders for patients with chronic kidney disease who require treatment for hyperphosphataemia.

6. Comparator

Appropriately, the submission nominated calcium carbonate as the main comparator. This is as previously agreed by the PBAC.

7. Clinical Trials

Updated data for the RIND Trial were presented in this submission consisting of follow-up data for an additional 13 (of 148) patients. No new data were presented for the DCOR Trial. Coronary artery calcification data from the RIND Trial and Treat-to-Goal Study were unchanged from the previous submission. A third trial of coronary artery calcification, the CARE-2 Study (2), was described but the results provided were preliminary.

A systematic review of observational prospective cohort studies relating vascular calcification and mortality was also presented.

The RIND trial had been published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
RIND		
Block GA et al 2005	Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis.	Kidney International. 68(4): 1815-1824.
Block GA et al 2007	Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients,	Kidney International. Advance Online Publication.
Galassi A et al 2006	Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium binders.	Nephrology Dialysis Transplantation 21: 3215-3222
Spiegel DM et al 2006	Calcium containing phosphate binders are associated with increased mortality risk in hemodialysis patients compared to sevelamer.	XLIII Congress of the European Renal Association (ERA)/European Dialysis and Transplant Association (EDTA). July 15-18 2006 Glasgow, United Kingdom.

The DCOR study had not been published at the time of submission.

8. Results of Trials

In the unpublished DCOR trial, there was no statistically significant difference in all-cause mortality for the whole population between sevelamer and calcium-based phosphate binders. A sub-group analysis of the DCOR study by age showed a borderline statistically significant difference in all-cause mortality favouring sevelamer over calcium-based phosphate binders in adults ≥65 years old (18.4 versus 23.6 deaths per 100 patient years; HR = 0.78, 95% CI 0.62- 0.97). In the RIND trial, mortality was not the primary analysis however the result was statistically significant (p=0.02). The uncertainty about the DCOR trial – 65 and older population result remained, given the lack of significance of the full population analysis. There was also uncertainty regarding the RIND trial result, given the small size, missing data, and mortality not being the primary outcome.

The re-submission supplied an analysis of observational studies that supported the role of vascular calcification as a risk factor for mortality, and this analysis was used by the submission to argue for the plausibility of the mortality treatment effect. The submission also provided data from the RIND trial showing an association between baseline coronary artery calcification and survival.

The re-submission presented one additional trial with toxicity data, but no different or new conclusions emerged from this. There remained a statistically significantly greater occurrence of dyspepsia associated with sevelamer, but no statistically significant difference in the occurrence of any gastrointestinal adverse events.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The resubmission described sevelamer as having significant advantages in effectiveness over calcium and having similar or less toxicity.

The PBAC accepted this claim.

10. Economic Analysis

An updated preliminary economic evaluation was presented using the updated data from the RIND Trial.

The trial-based incremental cost/extra life year saved for the base case was > $200,000 for the intent to treat population and in the range $45,000 – $75,000 for the sub-group of patients ≥ 65 years in the DCOR trial populations, similar to the previous re-submission. The base case estimate, for the RIND trial, was in the range $15,000 – $45,000, similar to the previous re-submission. The sensitivity analyses showed the ICERs were sensitive to estimates of the treatment effect.

An updated modelled economic evaluation was presented that incorporated the updated RIND trial data, dosing data from the RIND trial, the decreased sevelamer cost, and updated costs for hospitalisations and management of dyspepsia.

The base case modelled incremental discounted cost/extra life year saved was estimated to be in the range $15,000 – $45,000 for both the DCOR trial – 65 and older population model and the RIND trial population model.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be < 10,000 in Year 4, similar to the previous re-submission.

The financial cost/year to the PBS was estimated to be in the range $30 – $60 million in Year 4, similar to the previous re-submission.

12. Recommendation and Reasons

The PBAC recommended the listing of sevelamer on the PBS for the treatment of hyperphosphataemia in adults with chronic kidney disease on dialysis, on the basis of acceptable cost-effectiveness compared to calcium in the context of a high clinical need in a disease where the all cause mortality is currently around 10 percent per year. The estimated incremental cost-effectiveness ratios per life year gained are in the range $15,000 – $45,000 based on the DCOR trial 65 and older population and RIND trials.

The PBAC recalled that in its previous consideration of sevelamer, the pivotal uncertainties which led to the rejection of the application were whether the reduction in calcification reported for sevelamer was an appropriate surrogate measure to predict mortality, and the extent of mortality benefit with sevelamer. As part of its current deliberations, the PBAC took account of information provided by expert clinicians at a meeting held following the March 2007 PBAC meeting and which included discussion on the appropriate surrogate outcomes and whether age was a treatment effect modifier. Therefore, while the PBAC is aware that there are no randomised controlled trial data to prospectively validate calcification as a surrogate for mortality in this patient group, it accepted that the data suggest coronary

calcification may be a reasonable surrogate outcome for mortality, and noted the views of the Independent Expert Panel of Nephrologists.

The PBAC further noted the submission had offered a reduction in price compared with the previous submission. This price reduction helped further address the Committees' previous uncertainty about the cost-effectiveness of treatment.

The PBAC noted that although the current submission included data from an additional 13 of the 148 patients randomised to the RIND trial, the appearance of the survival curves and the final p-value differ only very little to those previously considered.

The PBAC further noted the analysis conducted for the sub-groups of the DCOR patients treated for less than 2 years versus those treated for 2 or more years, which, albeit, post-hoc showed that patients treated with sevelamer for more than 2-years had a significantly improved survival compared to those treated for less than 2 years.

The PBAC considered that inclusion of an age barrier in the listing restriction was not justified as no additional data to support treatment effect modification in patients over 65 years was presented. It noted the interaction was seen for the first time in one trial not designed (or powered) to detect it. This fact, together with the absence of a biological rationale is questionable evidence upon which to conclude that there is effect modification by age. Additionally, the validity of any subgroup analysis in a trial whose primary analysis has failed is questionable.

Extending the eligibility to patients not on dialysis with CKD-4 and CKD-5 stage renal disease, as recommended by the panel of nephrologists was not considered justified by the PBAC as no data had been evaluated on patients who were not on dialysis.

The Committee requested that any data from new clinical trials with sevelamer or which prospectively validate calcification as a surrogate for mortality in this patient group are presented to the PBAC as they become available.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation

SEVELAMER HYDROCHLORIDE, tablet, 800 mg

Restriction: Authority required
Hyperphosphataemia in an adult with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where:
(a) serum phosphate is greater than 1.6 mmol per L, or
(b) the serum calcium times phosphate product is greater than 4.0.

Maximum quantity: 180
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

Genzyme Australasia is pleased with the positive recommendation sevelamer has received and would like to thank all those involved with this decision. Genzyme Australasia will now work with the PBPA to expedite access of sevelamer to Australian dialysis patients.