PUBLIC SUMMARY DOCUMENT

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

Sponsor: Genzyme Australasia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission requested an authority required listing for the treatment of high phosphate levels (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 hyperphosphatemia, 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.

The PBAC agreed that, should listing proceed, an authority required listing is appropriate.

3. Registration Status

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

4. Listing Requested and PBAC's View

The re-submission proposed three PBS listings, with option 1 being the preferred wording.
Option 1
Authority required
Treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis.

Option 2- Alternative PBS indication.
Authority required
Treatment of hyperphosphataemia, in adult patients 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/L, or
(b) serum calcium x phosphate product is greater than 4.0 $mmol^2/L^2$.

Option 3 – Limited PBS indication.
Authority required
Treatment of hyperphosphataemia, in adult patients 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/L, or
(b) serum calcium x phosphate product is greater than 4.0 $mmol^2/L^2$,
and the patient is:

(a) aged ≥ 65 years, or
(b) new to dialysis, or
(c) an Aboriginal or Torres Strait Islander person.

The PBAC considered that the most restrictive of the proposed restrictions would be most likely to identify the population in whom treatment with sevelamer could be cost-effective ie option 3.

5. Clinical Place for the Proposed Therapy

Sevelamer would provide an alternative to calcium based phosphate binders for patients with chronic kidney disease who require treatment for hyperphosphatemia.

6. Comparator

The resubmission nominated calcium carbonate (Caltrate®) as the main comparator. This is as previously agreed by the PBAC.

7. Clinical Trials

The resubmission presented new trial data including the Statistical Analysis Plan and more detailed results for the Dialysis Clinical Outcomes Revisited (DCOR) trial, and a new trial, the RENAGEL In New Dialysis (RIND) study. The RIND study was a randomised, open-label, parallel group study of 114 adult patients new to haemodialysis.

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

Trial/First author	Protocol title/Publication title	Publication citation
RIND		
Spiegel DM, 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.
Block GA, 2005.	Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis.	Kidney International. 68(4): 1815–1824.

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

The resubmission also included seven supportive trials included in the previous submission, reporting biochemical outcomes and vascular calcification.

8. Results of Trials

Mortality was the primary outcome for the DCOR study. In the RIND study, all-cause mortality was a secondary endpoint of a randomised trial previously reported whose primary endpoint was change at 18 months in coronary artery calcification. For all evaluable patients in the RIND study the result for mortality was statistically significant. The results and epidemiological data showing vascular calcification was a risk factor for cardiovascular morbidity and mortality assumed that changes in vascular calcification with sevelamer would translate into changes in mortality and cardiovascular morbidity outcomes.

The RIND and Treat to Goal studies provided data on coronary artery calcium (CAC) scores. The change from baseline in CAC score was the primary end-point for the RIND study and a secondary end-point in the Treat to Goal study. The analysis showing all cause mortality is higher where CAC score is higher, provided no link between the surrogate and mortality.

The resubmission presented new toxicity meta-analyses demonstrating fewer hypercalcaemic episodes and more dyspepsia episodes in sevelamer treated patients, but overall no differences in all adverse gastrointestinal 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.

10. Economic Analysis

The resubmission presented updated preliminary economic evaluations, which included costs of hospitalisations and dyspepsia.

The re-submission estimated that the incremental cost effective ratios (ICERs) for the base case would be > $200,000 for the all population and in the range $45,000 – $75,000 for the ≥ 65 year old subgroup in DCOR.

The resubmission presented an updated modelled economic evaluation for two settings: The DCOR ≥ 65 year old population and the RIND population (patients new to dialysis) which included costs of hospitalisations and dyspepsia.

The resubmission estimated that the base case modelled incremental discounted cost per extra life year saved would be in the range $15,000 – $45,000 for the DCOR ≥ 65 year old population and in the range $15,000 – $45,000 for the RIND population.

11. Estimated PBS Usage and Financial Implications

The resubmission estimated that in Year 4 of listing the likely number of patients would be between 10,000 – 50,000 and the financial cost to the PBS would be in the range $30 – $60 million.

12. Recommendation and Reasons

The PBAC considered that the most restrictive of the proposed restrictions would be most likely to identify the population in whom treatment with sevelamer could be cost-effective, ie treatment of hyperphosphataemia, in adult patients 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/L, or (b) serum calcium x phosphate is greater than 4.0 $mmol^2/L^2$ and the patient is: (a) aged >65 years, or (b) new to dialysis, or (c) an Aboriginal or Torres Strait Islander person.

The PBAC considered that there are some doubts about the validity of the DCOR and RIND mortality results. The DCOR results relied on acceptance of a pre-specified subgroup analysis where the primary analysis was not statistically significant and acceptance that heterogeneity of a subgroup result implies effect modification by age. In the RIND study mortality was a pre-specified secondary endpoint and there were differential drop-out rates. The coronary artery calcification results involve substantial missing data, and no empirical data have been presented to support the assumption that vascular calcification changes with observed with sevelamer translate into cardiovascular benefits. The PBAC noted that the submission used the RIND study to validate the mortality difference in the less than 65 and over 65 sub-groups ie the mortality in RIND was being considered compatible with the over 65 sub-group in DCOR. The submission used the surrogate outcome of vascular calcification, which has been accepted in heart disease, for kidney disease.

The PBAC considered that the pivotal uncertainties were whether the reduction in calcification reported in the supportive trials, the RIND Study and the Treat to Goal Study was an appropriate surrogate measure to predict mortality, and the extent of mortality benefit with sevelamer.

The sponsor's Pre-PBAC Response reported statements from the CARI Guidelines (April 2006) purporting to support these claims, but the PBAC noted other statements in these Guidelines that cast doubt on such claims. For example the Shaheen et al study (2004) stated that "Mortality studies are needed to clarify the overall impact of sevelamer use". Comment on the Treat to Goal Study was that "Changes in vascular calcification may not be due to calcium use but related to other properties of sevelamer, such as lowered LDL-cholesterol". Further, the quote in the Pre-PBAC Response stating "reduced vascular and cardiac calcification (a surrogate measure for cardiac disease) with sevelamer holds promise for better patient management" was qualified with the words "however, at the time of the literature search no survival benefit had been established."

The PBAC concluded that although it was biologically plausible that reduction in calcification leads to a reduction in mortality, insufficient evidence had been provided in the submission to support the claim. Further, any reduction in mortality may be due to the ability of sevelamer to lower LDL-cholesterol.

Given the uncertainty about the extent of mortality benefit, there was uncertainty about the results of the modelled economic analysis, which were sensitive to the estimates of incremental survival.

Therefore, the PBAC rejected the submission because of uncertain clinical benefit and uncertain cost-effectiveness.

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 thanks the PBAC for its consideration in listing sevelamer hydrochloride. The company is disappointed in the rejection of its application. However, Genzyme remain committed to working with the PBAC to ensure its product is made available to those patients with end stage renal disease who may benefit from sevelamer.