

Public Summary Document

Product: Sevelamer hydrochloride, tablets, 800 mg, Renagel[®]
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: March 2006

1. Purpose of Application

The submission requested a Restricted Benefit listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products.

2. Background

This drug had not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Sevelamer has Therapeutic Goods Administration (TGA) marketing approval for the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease.

4. Listing Requested and PBAC's View

Restricted Benefit

Treatment of hyperphosphataemia, in adults patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where phosphate is greater than 1.8 mmol/L and where calcium x phosphate (CaXP) product is greater than 4.5 mmol/L.

See Recommendations and Reasons for PBAC's view.

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

The submission used a combination of calcium carbonate and calcium citrate as the main comparator in its economic evaluations whereas the Dialysis Clinical Outcomes Revisited (DCOR) Trial compared sevelamer and calcium-based phosphate binders (calcium acetate or calcium carbonate). The PBAC agreed that calcium was the appropriate comparator, but did not consider the calcium salt used was of relevance.

7. Clinical Trials

The submission presented one unpublished randomised controlled trial as the primary evidence i.e. the DCOR study. DCOR was a multi-centre, randomised, open-label, parallel design trial. At randomisation, patients were assigned to treatment with either sevelamer or a calcium-based phosphate binder and followed for up to 45 months. The study compared sevelamer with calcium and reported the clinical outcomes i.e. mortality, hospitalisation. This study had not been published at the time of submission.

Seven further short-term studies were included as supportive evidence, none of which evaluated mortality.

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In the unpublished DCOR trial, there was no statistically significant difference in all-cause mortality for the whole population between sevelamer and calcium-based phosphate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).

Sevelamer and calcium-based phosphate binders have different toxicity profiles. Sevelamer is more often associated with gastrointestinal adverse effects than calcium-based phosphate binders. For example, in one trial, a greater percentage of patients in the sevelamer group (16.2%) experienced dyspepsia compared with calcium-based phosphate binders (6.9%). Post-marketing surveillance (2000-03) showed an increase in the frequency of non-serious reports of flatulence and constipation. There were also reports of intestinal obstruction, ileus, sub-ileus and intestinal perforation. Calcium-based phosphate binders tend to cause more hypercalcaemia and cardiovascular calcification.

See Recommendations and Reasons for PBAC's view of these results.

9. Clinical Claim

The submission claimed that sevelamer is significantly more effective than calcium-based phosphate binders and has similar or less toxicity. The PBAC did not accept the submission's claim.

10. Economic Analysis

The submission presented a preliminary trial-based economic evaluation to determine a cost per life year gained. The incremental cost per extra discounted life year gained was estimated to be $> \$200,000$ for the intent to treat (ITT) population and $\$45,000 - \$75,000$ for the sub-group of patients ≥ 65 years.

The submission also presented a modelled economic evaluation. A cost-effectiveness analysis was performed to calculate the cost per life-year gained based on overall survival. In summary, the modelled evaluation extrapolated the survival estimates for 24 months beyond the trial period of 44 months. The incremental cost-effectiveness per life year gained was $\$75,000 - \$105,000$ under two different scenarios in the ITT population and $\$15,000 - \$45,000$ in the ≥ 65 years sub group.

The PBAC considered the submission's use of a cost-effectiveness approach to be inappropriate, given the conclusions about the lack of superiority of sevelamer over calcium-based phosphate binders (*see also Recommendations and Reasons*).

11. Estimated PBS Usage and Financial Implications

The financial cost to Government was estimated in the submission to be $\$10 - \30 million per year. The PBAC considered the estimates presented were highly uncertain for a number of reasons.

12. Recommendation and Reasons

The Committee agreed that, should listing proceed, an authority required listing is appropriate, noting that the sponsor had agreed to this prior to the meeting.

The PBAC advised that there was no statistically significant difference in all-cause mortality for the whole population between sevelamer and calcium-based phosphate binders in the key unpublished DCOR study. There were however some doubts if the study was adequately powered to detect such a difference. The study was designed with 1,000 patients per treatment arm so that it would have 80% power to detect a 22% decrease in all-cause mortality assuming a mortality rate of 20 per 100 patient-years in the calcium arm. One year after trial commencement, a planned interim analysis revealed that the death rate was 13.6 per 100 patient-years, substantially lower than what was anticipated. The data monitoring committee recommended extending the duration of study by one additional year. A posteriori power calculation was not however carried out to show the original power of the study was retained. In addition, it is unclear if the initial calculation gave allowances to the subsequent loss of follow-up and high drop-out rate. The PBAC thus considered it is likely that the trial remained underpowered for its primary analysis. If so, any subsequent sub-group analyses would also be underpowered.

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. The sponsor had informed the PBAC that this was a pre-specified subgroup analysis. However, it also clarified that the stratification of the randomisation by age was intended to ensure equivalent number of patients between the treatment groups within the age strata. Therefore, it was not intended for a formal test for interaction to ascertain whether the treatment effect varied based upon age. The pre-PBAC response failed to adequately address the issue of the large number of sub-group analyses undertaken and whether the p-value was adjusted for multiple sub-groups. Furthermore the PBAC considered was no biological plausibility for the argument that patients ≥ 65 years would experience a different treatment effect than the overall population. During the Cox regression analysis, significant interaction was only observed for all-cause mortality between treatment and age in the model ($p=0.03$). However, tests for heterogeneity were not conducted to show if the results in the sub-groups were statistically different from one another.

The PBAC also noted that although blood collection was not required for the study, biochemical data were obtained from the dialysis providers' central laboratories. Serum levels of phosphorus, calcium and calcium-phosphorus product were all similar between sevelamer and calcium-based phosphate binders.

Given that there were no statistically significant differences in all-cause mortality for the whole population between sevelamer and calcium-based phosphate binders nor in serum levels of phosphorus, calcium and calcium-phosphorus product, the PBAC did not accept the submission's description of sevelamer as having significant advantages in effectiveness over calcium-based phosphate binders.

Given the PBAC's conclusions about the lack of superiority of sevelamer over calcium-based phosphate binders, the PBAC considered the submission's use of a cost-effectiveness approach to be inappropriate.

Notwithstanding, the incremental cost effectiveness ratios derived from the model were considered by the Committee to be both high and uncertain. The PBAC had concerns about other issues of uncertainty with the modeled economic evaluation presented.

Thus, although PBAC acknowledged the need for an alternative product to the calcium and metal binders for treating hyperphosphataemia in adult patients with chronic kidney disease on dialysis, the submission was rejected because of a lack of convincing evidence of increased efficacy or safety overall, and a high 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

The sponsor, Genzyme Australasia will resubmit a new application for listing and will attempt to address each of the issues found by the PBAC in the first application. Genzyme Australasia seeks to work with the PBAC to ensure patients with end stage renal disease (ESRD) have PBS access to sevelamer.