Scottish Medicines Consortium

sevelamer hydrochloride, 800mg tablets (Renagel®) No. (423/07)
Genzyme Therapeutics Ltd

09 November 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sevelamer (Renagel®) is not recommended for use within NHS Scotland for control of hyperphosphataemia in adult patients receiving peritoneal dialysis.

It was non-inferior to a calcium-based phosphate binder in reducing serum phosphate and was associated with a lower rate of hypercalcaemia. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Control of hyperphosphataemia in adult patients receiving peritoneal dialysis. It should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy vitamin D_3 or one of its analogues to control the development of renal bone disease.

Dosing information

The starting dose (1-2 800mg tablets three times a day) in patients not on phosphate binders is based on serum phosphate levels, and in patients who are being changed it is based on the previous dose of calcium-based phosphate binders. The dose is then adjusted according to serum phosphate levels and may vary between 1 and 5 tablets per meal.

Date of licensing

The licence was changed on 1st June 2007 to include patients on peritoneal dialysis in addition to the existing indication for those on haemodialysis.

Summary of evidence on comparative efficacy

Hyperphosphataemia is a common complication in patients with end-stage renal disease. Sevelamer is a non-absorbed phosphate-binding polymer free of metal and calcium. Amines along the polymer spine become partially protonated in the intestine, attracting phosphate molecules, binding them in the gastrointestinal tract and lowering phosphate in the serum.

It has been compared with one other phosphate binding agent in an open-label, parallel design study which randomised 143 patients in a 2:1 ratio to sevelamer or calcium acetate. The trial recruited adult patients with chronic kidney disease (CKD) receiving peritoneal dialysis for 8 weeks or longer. At baseline, following a 2-week washout period for patients already taking phosphate binders, they were required to have serum phosphate >1.77 mmol/l.

The primary end point was the change from baseline at week 12 for serum phosphate, and the primary analysis was for non-inferiority of sevelamer to calcium acetate in a per-protocol population. Non-inferiority was concluded if the one-sided 97.5% confidence interval (CI) for the difference between sevelamer and calcium acetate was <0.3mmol/l. There was sub-group analysis of the primary end point for anuric and non-anuric patients and a secondary analysis with a full analysis set (all patients randomised who had received at least one dose of study drug and had at least one post-baseline assessment). Analyses of secondary and additional end points were also conducted with this data set. Secondary end points included the calcium/phosphate product and lipid profile, with serum albumin adjusted calcium as an additional end point.

The per protocol set included 72% (103/143) of patients randomised: 74% (72/97) and 67% (31/46) in the sevelamer and calcium acetate groups respectively. For the primary analysis in the sevelamer group, mean serum phosphate reduced from a baseline of 2.4 mmol/l to 1.9 mmol/l at treatment end, and there was a reduction from 2.3 to 1.8 mmol/l in the calcium acetate group. The mean change was -0.52 mmol/l and -0.58 mmol/l in each group respectively, and the difference in change [sevelamer – calcium acetate] was 0.061 mmol/l (97.5% upper CI: 0.237), meeting the criterion for non-inferiority. Similar reductions in serum phosphate were seen in the full analysis set and in sub-groups by anuria. Approximately half

of the patients in each group had serum phosphate levels within the upper limit of the United Kingdom Renal Association (UKRA) target range (1.8 mmol/L).

There was a significant decrease from baseline for calcium/phosphate product in both groups but the between-group difference was non-significant. In the sevelamer group it decreased from 5.7 $mmol^2/l^2$ at baseline to 4.5 $mmol^2/l^2$ at week 12, and the equivalent decrease in the calcium acetate group was from 5.7 $mmol^2/l^2$ to 4.6 $mmol^2/l^2$.

Serum albumin-adjusted calcium increased at study end from 2.38 mmol/l to 2.40 mmol/l in the sevelamer group and from 2.4 mmol/l to 2.5 mmol/l in the calcium acetate group. The difference from baseline was significant for calcium acetate but not sevelamer, and the between-group difference was significant.

For total, LDL- and non-HDL cholesterol there was a significant decrease from baseline with sevelamer but not calcium acetate, and the between-group difference was significant. HDL cholesterol changed very little in either group and triglycerides rose in both groups, but for both measures there was no significant differences between groups.

Summary of evidence on comparative safety

In the safety set (all patients randomised) there was no significant difference between the sevelamer and calcium acetate groups in the incidence of treatment-emergent or treatment-related adverse events (AE). Gastrointestinal disorders were the most common treatment-related AEs in both groups occurring in 27% (26/97) and 13% (6/46) of patients respectively. In the sevelamer group dyspepsia occurred in almost half of the patients with treatment-related gastro-intestinal AEs: 46% (12/26).

The incidence of hypercalcaemia, defined as albumin-adjusted serum calcium $\geq$2.75mmol/L, was significantly higher in the calcium acetate group than with sevelamer. Over the study period there were 5 cases of hypercalcaemia in 5 patients treated with calcium acetate, and none in the sevelamer group. This difference was also significant.

Treatment-emergent peritonitis occurred in eight patients (8.2%) in the sevelamer group and two (4.3%) in the calcium acetate group.

Summary of clinical effectiveness issues

The trial comparing sevelamer and calcium acetate was open-label. The clinical study report states that a number of factors made blinding impractical, and end-points were objective laboratory measures unlikely to be influenced by blinding.

In CKD there is a complex inter-relationship between serum phosphate, calcium and parathyroid hormone levels. Elevated levels of phosphate and calcium are associated with renal bone disease and other long-term adverse effects including increased mortality. High values for the product of calcium and phosphate are a marker for the risk of cardiovascular and other soft tissue calcification.

Both sevelamer and calcium acetate were similarly successful in achieving targets for serum phosphate and calcium/phosphate product and in each group about half of the patients achieved target phosphate levels. Serum albumin adjusted calcium levels rose significantly with calcium acetate compared with sevelamer (though mean levels were maintained within the normal range in both groups) and hypercalcaemia was significantly more common.

Compared with calcium acetate, sevelamer was associated with changes in lipid parameters which may be considered beneficial.

The incidence of adverse events was similar in both groups, though gastro-intestinal events such as dyspepsia were numerically more common with sevelamer. Peritonitis was more common in the sevelamer group. The difference was not significant and does not provide evidence of an association between sevelamer and peritonitis, but monitoring of new cases has been included in the risk management plan for two years post-licensing.

Summary of comparative health economic evidence

The manufacturer presented a 5-year cost utility analysis of sevelamer relative to calcium acetate. Both treatments had the same effect upon hyperphosphataemia. However, a difference between treatments arose from the higher serum calcium levels associated with calcium acetate treatment, as calculated from the key trial. Raised serum calcium levels were linked through values drawn from the literature to an increased mortality risk associated with calcium treatments. Given this, it may have been appropriate to also model an arm considering sevelamer as a second-line treatment for those patients experiencing raised calcium levels. In such a case, the additional treatment arm of second-line lanthanum carbonate could have been considered as a comparator.

In terms of costs, only the direct drug costs and monthly GP visits were included within the analysis. Dosing was based upon mid-trial actual dosing. The quality of life value for being alive and receiving peritoneal dialysis was taken from the literature. Adverse events were not modelled, which may have been a conservative approach.

At the end of the five years of the model it was anticipated that 33.4% of sevelamer patients would survive compared with 25.6% of calcium acetate patients. The led to a 0.16 QALY gain at an additional cost of £5,221 to give a cost effectiveness estimate of £31,836 per QALY. When the modelling was extended to a 10 year time horizon, the cost effectiveness estimate improved to £15,217 per QALY.

The main weaknesses of the analysis were:

- not having considered sevelamer as a possible second line therapy after calcium acetate, and related to this, not considering second line lanthanum carbonate;
- not considering possible sub-groups such as those with anuria for whom the effect upon serum calcium levels might differ;
- the base case quality of life for those undergoing peritoneal dialysis possibly being too high.

Given these limitations, the manufacturer did not demonstrate that sevelamer would be cost effective as a first-line treatment. As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

UK Renal Association guidelines for complications of chronic kidney disease define targets for a number of metabolic markers including serum phosphate (1.1 mmol/l to 1.8 mmol/l) and acknowledge that, in addition to dietary phosphate restriction, phosphate binders are usually required in late-stage disease.

US guidelines within the National Kidney Foundation Kidney Disease Outcomes Quality Initiative give a similar upper limit for phosphate, and advise that all available phosphate binders are effective in lowering serum phosphate and are suitable for use as primary therapy. They advise that daily intake of elemental calcium should not exceed 1500mg/day from calcium-based phosphate binders or 2000mg/day in total. Aluminium-based phosphate binders should be used for short periods only (4 weeks) in patients with hyperphosphataemia.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice in March 2007 that:

Lanthanum carbonate (Fosrenol®) is accepted for restricted use within NHS Scotland as a phosphate-binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis.

Lanthanum carbonate is as effective as calcium carbonate in reducing phosphate to target levels. It is restricted to use as a second-line agent in patients where a non-aluminium, non-calcium phosphate binder is required.

Additional information: comparators

Calcium carbonate, calcium acetate, dried aluminium hydroxide gel, lanthanum carbonate.

Cost of relevant comparators

Drug	Daily dose regimen	Cost per year (£)
Sevelamer (Renagel®)	**2.4 to 12g**	**745 to 3724**
Lanthanum carbonate (Fosrenol®)	750-3000mg	692 to 1957
Calcium acetate (Phosex®)	3 to 12 tablets	120 to 480
Calcium carbonate (Calcichew Forte®)	3 tablets	240
Aluminium hydroxide (Alu-cap®)	4 to 20 capsules	46 to 228
Calcium carbonate (Calcichew®)	3 to 6 tablets	102 to 204
Calcium carbonate (Adcal®)	3 to 6 tablets	79 to 158

Doses are for general comparison and do not imply therapeutic equivalence equivalence, and this is particularly true for these preparations which are titrated according to individual's needs. Costs from eVadis on 20th August 2007.

Additional information: budget impact

The manufacturer estimated a gross drug cost of sevelamer of £303k in year one, rising to £400k in year five. With an assumption that calcium acetate would be the drug displaced in line with the economic modelling, the net drug cost was estimated to be £131k in year one and £216 in year five. These estimates were based on data from the Scottish renal registry indicating a prevalence of 408 peritoneal dialysis patients and an annual incident population of 118. The company estimated a market share for sevelamer of 20% in year one rising to 35% by year five.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 12 October 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

European Medicines Agency (EMEA). European public assessment report (EPAR) for Renagel http://www.emea.europa.eu/humandocs/PDFs/EPAR/Renagel/Renagel-H-C-254-II-56%20-AR.pdf