

calcium acetate 435mg/magnesium carbonate 235mg tablet (Osvaren®) SMC No. (693/11)

Fresenius Medical Care

04 March 2011

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

ADVICE: following a full submission

calcium acetate 435mg/magnesium carbonate 235mg tablet (Osvaren®) is not recommended for use within NHS Scotland.

Indication under review: treatment of hyperphosphataemia associated with chronic renal insufficiency in patients undergoing dialysis (haemodialysis, peritoneal dialysis).

The combined preparation of calcium acetate/magnesium carbonate has been shown to reduce hyperphosphataemia associated with chronic renal disease.

However, 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

Treatment of hyperphosphataemia associated with chronic renal insufficiency in patients undergoing dialysis (haemodialysis, peritoneal dialysis).

Dosing Information

3 to 10 tablets daily depending on serum phosphate level. The daily dose should be divided according to the number of meals taken over the day (usually three). The starting dose is 3 tablets daily. If necessary the dose may be increased to a maximum of 12 tablets daily. It should be taken only with a meal and should not be crushed or chewed.

Product availability date

March 2009

Summary of evidence on comparative efficacy

Osvaren is a fixed dose oral formulation of calcium acetate 435mg/magnesium carbonate 235mg, which both bind phosphate within the gastrointestinal tract, thereby reducing phosphate absorption and the elevated serum phosphate levels that can occur in chronic kidney disease.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers use of this product when positioned for use in patients with hyperphosphataemia insufficiently controlled by calcium-containing phosphate binders alone or in whom there are concerns about calcification with calcium-containing phosphate binders.

In a single-blind study 255 adults undergoing haemodialysis or haemodiafiltration three times weekly who had hyperphosphataemia (serum phosphate ≥ 1.78 mmol/L) after wash-out of phosphate binders were randomised equally to calcium acetate/magnesium carbonate (Osvaren) or sevelamer hydrochloride for 24 weeks. The initial dose was at least four tablets daily and thereafter the dose was titrated to achieve serum phosphate below 1.78 mmol/L in the absence of hypercalcaemia or hypermagnesaemia. The average number of tablets per day in the calcium acetate/magnesium carbonate and sevelamer groups was 7.3 and 8.1, respectively, at week 25. The analysis of the primary endpoint, serum phosphate at week 25, was presented for a per protocol population that comprised all randomised patients who completed the study per protocol and included 105 patients who received calcium acetate/magnesium carbonate and 99 patients who received sevelamer. In the respective groups the numbers of patients discontinuing study treatment were 18 and 34. The primary endpoint was 1.70 and 1.77 mmol/L in the respective groups with a difference of -0.069 mmol/L. The corresponding one-sided 97.5% confidence interval of the difference was within the non-inferiority margin of 0.15 mmol/L. There was no significant difference in mean reduction in serum phosphate at week 25 between calcium acetate/magnesium carbonate and sevelamer: -0.76 and -0.71 mmol/L, respectively.

The secondary endpoints were assessed using last observation carried forward methodology in the full analysis population, which included all patients who were randomised, took study medication and had at least one subsequent efficacy evaluation. The area under the curve of serum phosphate was significantly lower in the calcium acetate/magnesium carbonate group compared with the sevelamer group with a difference of -24.5 mmol/L \times days. There were ten

assessment visits during the study. Calcium acetate/magnesium carbonate, compared with sevelamer, was associated with a significantly greater mean number of visits when target serum phosphate levels were achieved; 4.91 versus 3.96 visits (≤ 1.78 mmol/L) and 2.65 versus 1.81 visits (≤ 1.45 mmol/L). The mean times taken to achieve these targets were significantly shorter with calcium acetate/magnesium carbonate; 16 versus 30 days (for ≤ 1.78 mmol/L) and 57 versus 140 days (for ≤ 1.45 mmol/L).

An open-label study recruited 50 adults who had been receiving haemodialysis three times a week for two to five years and had been taking a calcium-containing oral phosphate binder for at least 12 months. They were randomised equally to calcium acetate/magnesium carbonate or calcium carbonate for 36 months. No primary outcome was specified. Within the calcium acetate/magnesium carbonate group, compared to the calcium carbonate group, serum phosphate and calcium levels were both significantly decreased and serum magnesium levels were significantly increased during the study. There were no figures for the magnitude of these differences. The authors note that further studies in larger numbers of patients are required to confirm these findings.

Summary of evidence on comparative safety

In the comparison of calcium acetate/magnesium carbonate with sevelamer the incidence of adverse effects was comparable between the groups. For adverse events judged to be related to study drug, gastrointestinal adverse events were more frequent with sevelamer compared to calcium acetate/magnesium carbonate: 24% versus 14%. Metabolism disorders, such as electrolyte disturbances, were more frequent with calcium acetate/magnesium carbonate compared to sevelamer. These were mainly episodes of asymptomatic hypermagnesaemia, 8.8% versus 2.4%. Mean changes from baseline to week 25 were significantly greater with calcium acetate/magnesium carbonate compared to sevelamer for serum calcium, 0.071 versus 0.004 mmol/L, and serum magnesium, 0.304 versus 0.043 mmol/L. The mean number of study visits where serum magnesium was greater than the upper limit of normal was significantly greater with calcium acetate/magnesium carbonate; 7.9 versus 4.1 study visits.

Summary of clinical effectiveness issues

As the constituents of calcium acetate/magnesium carbonate have been previously used for many years within this indication there was no requirement for the sponsor company to undertake a full clinical study to obtain a licence. Consequently calcium acetate/magnesium carbonate was granted European marketing approval on the basis that the constituents were already generally established for medicinal use with efficacy and safety acknowledged. Therefore, the clinical trials that usually accompany the licensing of a new medicine are not available. There were limited data presented and the reporting of the comparison with calcium carbonate did not allow a full understanding of the methodology of this study.

In the comparison with sevelamer the rationale for use of the per protocol population rather than the intention to treat population is not clear.

The submitting company has requested that the SMC considers the use of this product in a sub-population of the licensed indication, namely patients with hyperphosphataemia insufficiently controlled by calcium-containing phosphate binders alone or for whom there are concerns about

calcification with calcium-containing phosphate binders. This was not an inclusion criterion in the comparative studies described previously and the studies may have included patients with less severe hyperphosphataemia that was adequately controlled with calcium salts alone. Patients meeting the criteria for the company's proposed positioning may be less likely to achieve target phosphate levels and remain on treatment with this product compared to the study populations.

Calcium acetate/magnesium carbonate may have a role as a calcium sparing strategy and could potentially delay movement to more expensive non-calcium-containing phosphate binders. Clinical experts consulted note the potential benefits of calcium acetate/magnesium carbonate in a small number of patients who have low serum magnesium levels but also highlight the potential adverse consequences of use in patients with high serum magnesium levels.

Summary of comparative health economic evidence

The manufacturer submitted two implicit cost-minimisation analyses comparing the combination of calcium acetate/magnesium carbonate to 1) lanthanum carbonate and 2) sevelamer hydrochloride, for the treatment of patients with hyperphosphataemia after they have had treatment failure with calcium acetate or when there are concerns about calcification. A one year time horizon was chosen.

The clinical evidence used to support the assumption of non-inferiority compared to sevelamer hydrochloride came from a prospective, controlled, randomised, multi-centre study designed to compare tolerability and efficacy in haemodialysis patients. Non-inferiority was demonstrated.

No clinical evidence was presented to support equivalence with lanthanum carbonate, and therefore this was based on assumption.

The analyses compared the annual cost per patient treated with calcium acetate/magnesium carbonate to that with lanthanum carbonate and sevelamer hydrochloride. The costs were based on the drug acquisition cost associated with each and were reported for the lowest and highest daily dose of each treatment.

The results showed that the cost per year was £147 per patient treated with the lowest daily dose of calcium acetate/magnesium carbonate and £617 per patient treated with the lowest dose of lanthanum carbonate, equating to a saving of £470 per year with calcium acetate/magnesium carbonate. For the highest daily dose, the results showed the cost per year to be £588 and £1,963 per patient respectively, representing a saving of £1,375.

For the comparison with sevelamer hydrochloride, the results showed that the cost per year was £147 per patient treated with the lowest daily dose of calcium acetate/magnesium carbonate and £747 per patient treated with the lowest dose of sevelamer hydrochloride, equating to a saving of £600 per year with calcium acetate/magnesium carbonate. For the highest daily dose, the results showed the cost per year to be £588 and £3,734 per patient respectively, representing a saving of £3,146.

As such the manufacturer claimed that calcium acetate/magnesium carbonate would be the preferred treatment on cost-minimisation grounds versus the two selected comparators.

No sensitivity analyses were provided.

Limitations of the analysis include:

- The patients in the clinical study comparing calcium acetate/magnesium carbonate with sevelamer hydrochloride do not represent the patient population in the manufacturer's proposed positioning;
- Dose equivalence of phosphate binders in the subgroup is unclear. This patient group may be less likely to achieve target phosphate levels and remain on treatment with calcium acetate/magnesium carbonate compared to the wider study population;
- No clinical evidence was provided to demonstrate clinical equivalence with lanthanum carbonate, which is necessary as a basis for the cost-minimisation analysis approach used;
- Whilst it is possible that use of calcium acetate/magnesium carbonate as a calcium sparing strategy may delay movement to more expensive non-calcium based phosphate binders, no sequencing to further treatments was considered within the analysis.

Due to the limitations of the clinical evidence, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

In June 2008 the Scottish Intercollegiate Guidelines Network (SIGN) issued guideline number 103 on the diagnosis and management of chronic kidney disease. This makes no recommendations on particular phosphate binders for treatment of hyperphosphataemia.

In September 2008 the National Institute for Health and Clinical Excellence (NICE) issued clinical guideline number 73 on chronic kidney disease. This recommends measuring serum calcium, phosphate and PTH concentrations in people with stage 4 or 5 chronic kidney disease (GFR less than 30 ml/min/1.73m²) and determining the subsequent frequency of testing by the measured values and clinical circumstances. This makes no recommendations on particular phosphate binders for treatment of hyperphosphataemia.

In September 2010 the UK Renal Association published clinical practice guidelines on chronic kidney disease mineral and bone disorders. These recommend that in dialysis patients serum phosphate, measured before a "short-gap" dialysis session, should be maintained between 1.1 and 1.7 mmol/L.

They also note that there is insufficient data from randomised controlled trials that any specific oral phosphate binder impacts on individual patient outcome, and hence the choice of oral binders should be individualised, based on the effects of the available agents on a range of clinical parameters, especially avoidance of hypercalcaemia, rather than solely focused on serum phosphate alone.

The American Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that in chronic kidney disease patients with kidney failure stage 5 and those treated with

haemodialysis or peritoneal dialysis, serum levels of phosphorus should be maintained between 1.13 and 1.78 mmol/L. In patients with stage 5 kidney failure it is noted that both calcium-based phosphate binders and other noncalcium-, nonaluminium-, nonmagnesium-containing phosphate-binding agents (such as sevelamer hydrochloride) are effective in lowering serum phosphorus levels and either may be used as the primary therapy. In dialysis patients who remain hyperphosphataemic (serum phosphorus >1.78 mmol/L) despite the use of either of these, a combination of both should be used. The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day, and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcaemic (corrected serum calcium of >2.54 mmol/L), or whose plasma PTH levels are <16.5 mmol/L on 2 consecutive measurements. Non-calcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. In patients with serum phosphorus levels >2.26 mmol/L, aluminium-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. In such patients, more frequent dialysis should also be considered.

Additional information: comparators

Calcium carbonate (Calcichew, Calcichew Forte, Calcium 500 and Adcal), calcium acetate (Phosex and PhosLo), aluminium hydroxide (Alu-cap), sevelamer hydrochloride (Renagel), sevelamer carbonate (Renvela) and lanthanum carbonate (Fosrenol) can all be used to treat hyperphosphataemia. For the patient population in the submitting company's proposed positioning (i.e. those with hyperphosphataemia insufficiently controlled by calcium-containing phosphate binders alone or in whom there are concerns about calcification with calcium-containing phosphate binders) relevant comparators would be aluminium hydroxide, sevelamer hydrochloride, sevelamer carbonate and lanthanum carbonate.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Calcium acetate 435mg, magnesium carbonate 235mg (Osvaren)	3 to 12 tablets daily	146 to 582
Sevelamer carbonate 800mg (Renvela)	3 to 15 tablets daily	716 to 3,578
Sevelamer hydrochloride 800mg (Renagel)	3 to 15 tablets daily	716 to 3,578
Lanthanum carbonate 500mg (Fosrenol)	1.5g to 3g daily	1,385 to 1,957
Calcium acetate 1000mg (Phosex)	3 to 12 tablets daily	120 to 480
Calcium acetate 667mg (PhosLo)	6 to 12 tablets daily	157 to 314
Calcium carbonate 2500mg (Calcichew Forte)	3 tablets daily	240
Aluminium hydroxide 475mg (Alu-cap)	4 to 20 capsules daily	45 to 228
Calcium carbonate 1250mg (Calcium 500)	3 to 6 tablets daily	103 to 207
Calcium carbonate 1250mg (Calcichew)	3 to 6 tablets daily	102 to 204
Calcium carbonate 1500mg (Adcal)	3 to 6 tablets daily	79 to 158

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on date 9 December 2010.

Additional information: budget impact

The manufacturer has estimated that treatment with calcium acetate/magnesium carbonate will result in cost savings of £93k and £54k in year one, and £860k and £1.5m in year five, when compared to sevelamer hydrochloride and lanthanum carbonate, respectively.

These estimates assumed that 35 patients are treated with calcium acetate/magnesium carbonate in year one, rising to 557 by year five. These estimates appear to have been calculated based on market share prediction of 1.4% in year one rising to 20.4% in year five.

References

The undernoted references were supplied with the submission.

de Francisco ALM, Leidig M, Covic AC et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. *Nephrol Dial Transplant* 2010; 25: 3707-17

Deuber HJ. Long-term efficacy and safety of an oral phosphate binder containing both calcium acetate and magnesium carbonate in haemodialysis patients. *Nieren-und Hochdruckkrankheiten* 2004; 33(8):403-8.

This assessment is based on data submitted by the applicant company up to and including 11 February 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.