TRANSPARENCY COMMITTEE

OPINION

22 July 2009

PHOSPHOSORB 660 mg, film-coated tablet
Container of 200 (CIP: 381 466-0)

Applicant: FRESENIUS MEDICAL CARE FRANCE

Calcium acetate

List II

Date of Marketing Authorisation (mutual recognition): 7 September 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Calcium acetate

1.2. Indication
“Hyperphosphataemia in patients with chronic renal insufficiency undergoing dialysis”.

1.3. Dosage
“PHOSPHOSORB 660 mg should always be used with close monitoring (cf. SPC, “special warnings and precautions for use” section).

Adults: The recommended starting dose is two tablets (334 mg of calcium) three times daily. The dose is gradually increased until the desired serum phosphorus level is reached, provided that hypercalcaemia does not occur. Most patients require 3 to 4 tablets with each meal.

The dose may need to be adjusted either upwards or downwards, depending on phosphate intake or its elimination during dialysis.

Children and adolescents (less than 18 years of age): No sufficient information is available on the relationship of age to the effects of calcium acetate in paediatric patients. Therefore, Phosphosorb 660 mg cannot be recommended in these patients.

The elderly: A normal dosage regimen is recommended for the elderly. The tablets should only be taken together with meals to achieve the maximum phosphate binding effect. Tablets should preferably be swallowed whole. When a patient has difficulty swallowing the tablet due to its size, the tablet can be broken in half along the score line and the two halves swallowed one after the other. In that case the tablets need to be divided in two just before ingestion to avoid the development of a taste of acetic acid. In the event of a missed dose, the next dose should be taken at the normal time (no attempt should be made to make up for the missed dose).”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2008)
A : Alimentary tract and metabolism
A12 : Mineral supplements
A12A : Calcium
A12AA : Calcium acetate anhydrous

2.2. Medicines in the same therapeutic category
Calcic phosphate binders (calcium carbonate):
- Calcidia 1.54 g, granules for oral suspension in sachets
- Eucalcic 1.2 g/15 ml, oral suspension in sachets

2.3. Medicines with the same therapeutic aim
Aluminium salt (carbonate gel/aluminium hydroxide): Lithiagel oral suspension
Lanthanum carbonate: Fosrenol (250, 500, 750 and 1000 mg), chewable tablet.
Sevelamer: Renagel 800 mg, film-coated tablet
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy and tolerance

The company supplied 18 studies.

- one study versus placebo (Emmett 1991¹),
- five studies versus sevelamer (Hervas 2003², Qunibi 2004³ and 2008⁴, Bleyer 1999⁵ and Brewster 2006⁶). The study Brewster 2006⁶, a retrospective study of medical data, will not be examined in this opinion.
- a study versus lanthanum carbonate (Finn 2008⁷). In this study lanthanum carbonate was compared with other hypophosphataemic treatments. In the absence of any direct comparison (specific subgroup analysis) between the different hypophosphataemic treatments, notably calcium acetate (PHOSPHOSORB), this study will not be examined in this opinion.
- eight studies versus calcium carbonate (Schaefer 1991⁸, Delmez 1992⁹, Caravaca 1992¹⁰, Ring 1993¹¹, Ben Hamida 1993¹², Pflanz 1994¹³, Almirall 1994¹⁴, Conolly 1995¹⁵),
- one study versus aluminium hydroxide (Janssen 1996¹⁶).

Two paediatric studies were also supplied (the studies Pieper 2006¹⁷ and Wallot 1996¹⁸). Since the marketing authorisation does not recommend the use of PHOSPHOSORB in children and adolescents, these studies will not be examined in this opinion.

These studies were all carried out on patients with chronic renal insufficiency undergoing dialysis.

Only comparative studies versus placebo or an active comparator in which the statistical tests were carried out between the compared groups and which included more than 30 patients will be examined in this opinion. Applying these criteria, 8 studies were considered. Their methodologies and their main results are presented in the enclosed table.

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Since the primary and secondary criteria were not clearly identified and uniform from one study to another, only the results for phosphataemia (S-PO₄) and the occurrence of hypercalcaemia will be presented (cf. annex). The large number of assessment criterion with the lack of hierarchical organisation make difficult to interpret the results.

Note: Hypercalcaemia in renal insufficiency is a risk factor for overall mortality¹⁹

3.2. Conclusion

The assessment of the efficacy and safety of PHOSPHOSORB is based on 8 studies versus placebo, sevelamer and calcium carbonate. Most of these studies are open ones with a low number of patients and on a short follow-up periods (few weeks), except for the studies Qunibi 2008 and Janssen 1996 (1 year).

Study versus placebo:

In the study Emmett 1991, a significant reduction in phosphataemia (S-PO₄) was observed with calcium acetate (PHOSPHOSORB) in comparison to placebo.

Studies versus sevelamer:

In the studies Hervas 2003 and Bleyer 1999, no significant difference in terms of decrease of S-PO₄ was demonstrated between the groups treated with calcium acetate (PHOSPHOSORB) and sevelamer. A significantly larger number of cases of hypercalcaemia was observed with calcium acetate than with sevelamer:

- Hervas 2003 study: 8.9% versus 7.1% (NS),
- Bleyer 1999 study: 27% versus 5%, p < 0.0001.

In the study Qunibi 2004, a significant decrease of S-PO₄ was shown with calcium acetate versus sevelamer (difference -1.08 mg/dl, p = 0.0006) combined with an increase in calcaemia (S-Ca) (difference 0.63 mg/dl, p < 0.0001).

In the study Qunibi 2008, the non-inferiority of calcium acetate by comparison with sevelamer was demonstrated by the coronary artery calcification score.

Studies versus calcium carbonate:

In the study Janssen 1996, no significant difference in terms of decrease of S-PO₄ was demonstrated between the groups treated with calcium acetate (PHOSPHOSORB) and calcium carbonate. A significantly larger number of cases of hypercalcaemia was observed with calcium carbonate than with calcium acetate (31% versus 18%).

In the study Conolly 1995, no significant difference in terms of the decrease of S-PO₄ was demonstrated between the groups treated with calcium acetate (PHOSPHOSORB) and calcium carbonate. This study showed a lower intake of elemental calcium under calcium acetate than under calcium carbonate, without demonstrating a difference in terms of active absorption of calcium. Moreover, this reduced intake of elemental calcium observed with calcium acetate was associated with a less good digestive tolerance than with calcium carbonate.

Finally, a significantly larger number of cases of hypercalcaemia was observed with calcium carbonate than with calcium acetate (11/32 patients versus 4/32 patients).

In the study Pflanz 1994, a significant decrease of S-PO$_4$ was demonstrated with calcium acetate (PHOSPHOSORB) versus calcium carbonate: 1.51 ± 0.65 mmol/l vs. 1.80 ± 0.50, p < 0.005. Hypercalcaemia was observed in 2 patients in the calcium acetate group; no hypercalcaemia was observed in the calcium carbonate group.

The adverse effects more commonly observed with calcium acetate were: hypercalcaemia, nausea, vomiting, diarrhoea and constipation.

No study are available on the comparison of the efficacy of calcium acetate (PHOSPHOSORB) with lanthanum carbonate (Fosrenol), as the main target. There is also no study on calcium acetate in patients undergoing peritoneal dialysis.

### 4. TRANSPARENCY COMMITTEE CONCLUSIONS

#### 4.1. Actual benefit

Hyperphosphataemia can, mainly because of its osseous and cardiovascular complications, be serious for patients with chronic renal insufficiency.

PHOSPHOSORB is intended as a preventive treatment.

The efficacy/adverse effects ratio for this medicinal product in this indication is high.

This medicinal product is a first-line therapy.

There are treatment alternatives, mainly calcium carbonate, lanthanum carbonate and sevelamer.

**Public health benefit:**

Hyperphosphataemia is common in patients with chronic renal insufficiency. While it is accepted that hyperphosphataemia is associated with an increased risk of morbidity, its impact on mortality has not been established. Consequently, the burden of the disease cannot be quantified.

The therapeutic need is at least partially covered by existing medicines (Fosrenol, Renagel and calcium salts).

The available clinical data do not allow an assessment to be made of the impact of PHOSPHOSORB on morbidity and mortality linked to hyperphosphataemia as opposed to the comparison medicines.

The actual benefit of PHOSPHOSORB is substantial.

#### 4.2. Improvement in actual benefit (IAB)

PHOSPHOSORB (calcium acetate) does not provide any improvement in actual benefit (IAB V) in the management of patients with chronic renal insufficiency undergoing dialysis who have hyperphosphataemia.

#### 4.3. Therapeutic use

In patients with chronic renal insufficiency undergoing dialysis, hyperphosphataemia is associated with an increased risk of morbidity (Block, 1998 et 2000), particularly osseous and cardiovascular.
Despite the possibility of control of the phosphate serum levels by the diet and dialysis, most of these patients need to take phosphate-binding medications. In this situation, patients may benefit from treatments such as calcium salts, sevelamer or lanthanum carbonate.

4.4. Target population

The target population for PHOSPHOSORB consists of dialysed patients with chronic renal insufficiency and hyperphosphataemia.

The number of patients with chronic renal insufficiency undergoing haemodialysis or peritoneal dialysis can be estimated at about 31,000 (Rapport REIN 2007) in France.

According to experts, between 70% and 95% of them, i.e. between 20,000 and 30,000 patients, have hyperphosphataemia requiring therapeutic management.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage regimen stated in the marketing authorisation.

Packaging: Appropriate for the prescription conditions
Reimbursement rate: 65%

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## Annex – Summary of studies

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<tr>
<th>Study</th>
<th>Method</th>
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<th>Treatments</th>
<th>Results</th>
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<td>Emmett, 1991</td>
<td>Prospective sequential study in 2 parts</td>
<td>Adult CRI patients receiving haemodialysis 3 times a week</td>
<td>Part A: CaAc, n = 91&lt;br&gt;CaAc: n = 36&lt;br&gt;Pbo: n = 32&lt;br&gt;Mean age: 55 years</td>
<td>After 14 weeks:</td>
<td>Five cases of transient moderate hypercalcaemia under CaAc</td>
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<td></td>
<td>Part A: Open, 1 single arm (CaAc) (12 weeks)&lt;br&gt;Part B: Controlled versus placebo, randomised, double-blind crossover (2 weeks)</td>
<td><strong>Efficacy endpoints:</strong> S-PO₄, S-Ca</td>
<td><strong>Part B:</strong>&lt;br&gt;Part B: n = 68&lt;br&gt;CaAc: n = 36&lt;br&gt;Pbo: n = 32</td>
<td>- S-PO₄: -0.52 mmol/l under CaAc vs. +0.23 mmol/l under Pbo, p &lt; 0.01&lt;br&gt;- S-Ca: +0.15 mmol/l under CaAc vs. -0.05 mmol/l under Pbo.</td>
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<tr>
<td>Hervas, 2003</td>
<td>Randomised comparative study of CaAc vs. sevelamer</td>
<td>Adult patients receiving haemodialysis 3 times a week for ≥ 3 months</td>
<td>Sevelamer, n = NA&lt;br&gt;CaAc, n = NA&lt;br&gt;Mean age: 60.4 ± 15.1 years</td>
<td>After 34 weeks</td>
<td>At least 1 episode of hypercalcaemia in 8.9% of patients on CaAc and 7.1% of patients on sevelamer (NS)</td>
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<td></td>
<td><strong>Efficacy endpoints:</strong> S-PO₄</td>
<td><strong>S-PO₄:</strong> decrease greater with CaAc vs. sevelamer, difference -1.6 ± 0.1 mg/dl (-21.3%) under CaAc vs. -2.29 ± 0.05 mg/dl (-28.3%) under sevelamer, NS</td>
<td></td>
<td><strong>S-Ca:</strong> Increase greater with CaAc vs. sevelamer, difference 0.63 mg/dl, p &lt; 0.0001&lt;br&gt;Ca x P: decrease greater with CaAc vs. sevelamer, difference 6.1 mg²/dl², p &lt; 0.0001</td>
<td>Incidence of AEs identical in the 2 groups&lt;br&gt;Commonest AEs: diarrhoea (38 vs. 36%), constipation.</td>
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<td>Qunibi, 2004 (CARE)</td>
<td>Randomised, double-blind comparative study of CaAc vs. sevelamer</td>
<td>Adult patients receiving haemodialysis for ≥ 3 months</td>
<td>Sevelamer, n = 50&lt;br&gt;CaAc, n = 48&lt;br&gt;Mean age: 53.1 ± 14.0 years</td>
<td>After 8 weeks</td>
<td>Significantly more hypercalcaemia with CaAc vs. sevelamer: OR 6.1 [2.8; 13.3], p &lt; 0.0001</td>
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<td></td>
<td><strong>Efficacy endpoints:</strong> Ca x P, S-PO₄, S-Ca</td>
<td><strong>S-PO₄:</strong> decrease greater with CaAc vs. sevelamer, difference -1.08 mg/dl, p = 0.0006&lt;br&gt;<strong>S-Ca:</strong> Increase greater with CaAc vs. sevelamer, difference 0.63 mg/dl, p &lt; 0.0001&lt;br&gt;Ca x P: decrease greater with CaAc vs. sevelamer, difference 6.1 mg²/dl², p &lt; 0.0001</td>
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<td>Incidence of AEs, particularly gastrointestinal, identical in the 2 groups</td>
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**Abbreviations:**
- S-Ca: Serum calcium
- S-PO₄: Serum phosphate
- CaAc: Calcium acetate
- Ca x P: Calcium-phosphate ratio
- HD-Ca: Ca in the dialysate
- CRI: Chronic renal insufficiency
- Pbo: placebo
- NA: Not available
- ATV: Atorvastatin
- PTH: Parathormone
- NS: Not significant
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<td><strong>Studies versus sevelamer</strong></td>
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<td>Qunibi, 2008 52 weeks (CARE-2)</td>
<td>To test the hypothesis that the progression of calcification is identical in haemodialysis patients treated with CaAc or with sevelamer when LDL-C is reduced to the target level of &lt;70 mg/dL (&lt;1.81 mmol/L)</td>
<td>Adult patients receiving chronic haemodialysis for &gt;3 months (and ≤5 yrs) S-PO₄ &gt; 5.5 mg/dL</td>
<td>CaAc + atorvastatin, n = 103 91% of patients on atorvastatin  Sevelamer ± atorvastatin n = 100 79% of patients on atorvastatin</td>
<td>After 52 weeks: mean increase in CAC of 35% on CaAc vs. 39% on sevelamer, with an adjusted ratio for the CaAc/sevelamer covariate of 0.994, 95% CI [0.851-1.161] &lt; 1.8 → Non-inferiority demonstrated</td>
<td>Incidence of AEs identical in the 2 groups. Commonest AEs: diarrhoea (16 vs. 16%), nausea (17 vs. 17%), vomiting (17 vs. 18%).</td>
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<td>Bleyer, 1999 2 x 8 weeks</td>
<td>Comparative randomised, open crossover study of CaAc vs. sevelamer</td>
<td>Adult patients undergoing haemodialysis S-PO₄ &gt; 6 mg/dL</td>
<td>CaAc, n = NA  Sevelamer, n = NA</td>
<td>No significant difference (NS) in terms of the decrease of S-PO₄, Ca x P S-Ca: Increase with CaAc vs. sevelamer (0.2 mg/dl vs. 0.6 mg/dl, p &lt; 0.0001</td>
<td>Incidence of AEs identical in the 2 groups. At least 1 episode of hypercalcaemia in 27% of the patients with CaAc compared to 5% with sevelamer (p &lt; 0.0001).</td>
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<td><strong>Study versus calcium carbonate</strong></td>
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<td>Pflanz, 1994 2 x 6 weeks</td>
<td>Randomised, open, crossover comparative study of CaAc vs. CaCO₃ performed in a single centre</td>
<td>Adult chronic haemodialysis patients</td>
<td>CaAc, n = 31  CaCO₃, n = 31</td>
<td>S-PO₄: Larger decrease of CaAc vs. Ca CO₃: 1.51 ± 0.65 vs. 1.80 ± 0.50 mmol/l, p &lt; 0.005 S-Ca: Increase with CaAc vs. CaCO₃: 2.40 vs. 2.32 mmol/l, p&lt;0.005</td>
<td>Treatment stopped due to GI disorders: 2 patients with CaAc vs. 1 on CaCO₃ S-Ca &gt;2.70 mmol/l in 2 patients with CaAc and 6 of mild hypercalcaemia</td>
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<td>Connolly, 1995 12 weeks</td>
<td>Randomised, double-blind crossover comparative study of CaCO₃ vs. CaAc</td>
<td>Adult chronic haemodialysis patients</td>
<td>CaAc, n = 32  CaCO₃ n = 32</td>
<td>S-PO₄: No significant difference (NS) in terms of the decrease of S-PO₄ S-Ca: No significant difference (NS) in terms of the decrease of S-Ca.</td>
<td>Hypercalcaemia: 4 patients with CaAc vs. 11 on CaCO₃ Treatment stopped due to GI adverse effects: 5 patients with CaAc</td>
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<td>Janssen, 1996 12 months</td>
<td>To evaluate the efficacy of Al(OH)₃, CaCO₃ and CaAc in haemodialysis patients. Prospective open, randomised comparative study of Al(OH)₃ [3 months] vs. then CaAc [9 months] vs. CaAc vs. CaCO₃</td>
<td>Adult chronic haemodialysis patients</td>
<td>Al(OH)₃ [3 months] vs. then CaAc [9 months], n = 15  CaAc, n = 18  CaCO₃, n = 20</td>
<td>S-PO₄: No significant difference (NS) in terms of the decrease of S-PO₄ between CaAc and CaCO₃ taken preprandially S-Ca: Non-inferiority demonstrated between the two salts</td>
<td>Hypercalcaemia: 18% with CaAc (18%) vs. 31% with CaCO₃</td>
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