HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 March 2012

OSVAREN 435 mg/235 mg, film-coated tablet
Bottle of 180 (CIP: 382 886 3)

Applicant: FRESENIUS MEDICAL CARE FRANCE

calcium acetate/magnesium carbonate

ATC code: V03AE04 (drug for treatment of hyperkalemia and hyperphosphatemia)

List II

Date of Marketing Authorisation (mutual recognition): 14 December 2007

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Calcium acetate
Magnesium carbonate

1.2. Indication

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

1.3. Dosage

Adults:

Three to ten film-coated tablets a day, depending on the serum phosphate level. The daily dose should be divided according to the number of meals taken over the day (usually three a day).

The recommended starting dose is three tablets per day.

The dose may be increased to a maximum of twelve film-coated tablets a day if necessary.

To achieve the maximum phosphate binding effect, OSVAREN® should be taken only with a meal and should not be crushed or chewed.

For easy swallowing, the tablets should be taken with some liquid at the same time. If the patient gets difficulties to swallow the tablet because of its size, it should be broken along the score line immediately before ingestion to avoid the development of taste of acetic acid.

Because the rate or extent of absorption of other medicinal products administered orally may vary when used concurrently with OSVAREN®, no other oral medicinal products should be taken within a 2-hour period before nor 3 hours after administration of OSVAREN® (see section 4.5 of the SmPC).

In case of a missed dose, the next dose should be taken at the usual time (do not take an additional dose to make up for the missed dose).

OSVAREN can be prescribed of long-term period.

Children and adolescents (aged below 18 years):

No available data regarding the use of OSVAREN in such patients.

Consequently, OSVAREN is not recommended in these patients (see section 4.4 of the SPC)."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

V	: various
V03	: all other medicines with a similar therapeutic aim
V03A	: all other medicines with a similar therapeutic aim
V03AE	: drugs for treatment of hyperkalemia and hyperphosphatemia
V03AE04	: calcium acetate and magnesium carbonate

2.2. Medicines in the same therapeutic category

These are the other calcium chelating agents used in the treatment of hyperphosphatemia associated with chronic kidney disease:

- calcium carbonate: CALCIDIA (from BAYER), EUCALCIC (from NYCOMED) ***(substantial AB)***,

- calcium acetate: PHOSPHOSORB (from Fresenius Medical Care) ***(opinion of 22/07/2009: substantial AB, IAB V)).***

2.3. Medicines with a similar therapeutic aim

Lanthanum carbonate:

- FOSRENOL (from SHIRE) (250, 500, 750 and 1000 mg), *chewable* tablet ***(opinion of 12/04/2006: substantial AB, IAB V/sevelamer).***

Sevelamer:
- RENAGEL (from GENZYME) ***(opinion on inclusion of 18/12/2002: substantial AB, IAB II / calcium salts – opinion on renewal of inclusion of 11/06/2008: substantial AB / IAB V),***
- RENVELA (from GENZYME) ***(opinion of 21/10/2009: substantial AB, IAB V)***.

3. ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and tolerance of OSVAREN® relies on:

- a phase III clinical study (CALMAG-01[1]), whose goal was to establish the non-inferiority of OSVAREN with regard to sevelamer (RENAGEL) in terms of the serum phosphate levels in dialysis patients with kidney disease.
- a supporting study[2], whose aim was to compare the efficacy of OSVAREN in comparison to calcium carbonate in terms of the blood phosphate and calcium levels in haemodialysis patients.

In support of its application, other studies were quoted:

- 8 clinical studies on calcium acetate as monotherapy (Emmett 1991, Hervas 2003, Qunibi 2004 and 2008, Bleyer 1999, Plflanz 1994, Conolly 1995 and Janssen 1996),
- 4 studies on magnesium carbonate as monotherapy (Tzanakis 2008, Spiegel 2007, Delmez 1996 and O'Donovan 1986).

The interest of the combining the two active ingredients as contained in Osvaren was not demonstrated in these studies.

Finally, the company cited some studies to prove benefits of magnesium as a means of reducing phosphorus, reducing the amounts of calcium delivered to the patient, PTH levels, arterial calcifications, the intima media thickness, and so on, which, because of their poor methodology (including expert opinions, small patient populations, open studies, *in vitro* studies, etc.), do not allow any conclusion,.

3.1. Efficacy

3.1.1. Study CALMAG-01

Method: Randomised, single-blind (masked investigator), parallel-group, non-inferiority study of OSVAREN versus RENAGEL (sevelamer hydrochloride) in 244 patients on haemodialysis or online haemodiafiltration, followed up for 24 weeks.

Non-inferiority was met if the upper limit of the confidence interval did not exceed the limit fixed at 0.15 mmol/l.

Inclusion criteria: patients aged 18 to 85 years, stable, on thrice-weekly haemodialysis or online haemodiafiltration for at least the previous 3 months and ongoing, and:
- willing to continue with their diet for the duration of the study,
- with a serum phosphate level ≥ 1.78 mmol/l (5.5 mg/dl) after the 2-week washout period,
- not need any vitamin D-based treatment or calcimimetics or under treatment for at least 1 month,
- with a life-expectancy not less than the duration of the study.

1 De Francisco et al. Evaluation of calcium acetate / magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodyalisis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrol Dial Transplant (2010) 25:3707-17.
2 Deuber et al. Long-term efficacy and safety of an oral phosphate binder containing both calcium acetate and magnesium carbonate in haemodialysis patients. Nieren Hochdruck 2004;33:403-8.

Treatment:

During the pre-inclusion period (2 to 3 weeks), all patients pre-treated with phosphate chelating agents stopped their treatment and were then randomised into two groups:

- OSVAREN (calcium acetate 435-468 mg, magnesium carbonate 235 mg), n = 122 (*105 of them per protocol*),

- RENAGEL 800 mg, n = 122 (*99 of them per protocol*).

The starting dose for the two treatments was at least 4 tablets a day; the dose was then increased gradually by 2-3 tablets/day to reach and remain at a serum phosphate level < 1.78 mmol/l (5.5 mg/dl) until the end of the study.

Primary efficacy endpoint: Serum phosphate level after 25 weeks of treatment.

Secondary endpoints: Serum calcium and magnesium levels after 25 weeks of treatment.

RESULTS:
The characteristics of the patients in each group were comparable on inclusion. Patients in the OSVAREN group were older than in the RENAGEL group: 59.2 ± 13.72 years versus 55.9 ± 11.75 years.

Serum phosphate level after 25 weeks of treatment.

	OSVAREN (calcium + magnesium) Mean ± SD	**RENAGEL** (sevelamer hydrochloride) Mean ± SD	**Difference OSVAREN vs RENAGEL**
PP analysis mmol/l	n = 105 1.704 ± 0.4806 [0.87; 3.04]	n = 99 1.7069 ± 0.6066 [0.59; 3.93]	-0.0693 97.5% CI(-∞; 0.0692]

After 25 weeks, the upper limit of the observed confidence interval was 0.0692, i.e. below the limit fixed by the protocol [0.15 mmol/l]. The non-inferiority of OSVAREN versus RENAGEL in terms of the serum phosphate level was proven.
ITT analysis confirms the observed *per protocol* results.

Secondary endpoints:
After 24 weeks of treatment a significant increase was observed in the OSVAREN group versus RENAGEL in terms of:

- serum calcium level: 0.071 ± 0.1790 mmol/l versus 0.004 ± 0.1522 mmol/l, difference 0.0477 mmol/l, 95% CI [0.0162; 0.0793], p = 0.0032,
- serum magnesium level: 0.304 ± 0.2285 mmol/l versus 0.043 ± 0.1453 mmol/l, difference 0.2597 mmol/l, 95% CI [0.2137; 0.3056], p < 0.0001.

3.1.2. Deuber Study 2004[2]

Method: Open, randomised comparative study (calcium acetate 435 mg + magnesium carbonate 235 mg versus calcium carbonate 500 mg), performed in 50 CKD and HD patients for the previous 18 to 36 months, followed-up for 36 months.
Before inclusion in this study, a 1-year retrospective phase was carried out during which all patients were treated with calcium carbonate 500 mg.

Treatment:

- Calcium acetate 435 mg + magnesium carbonate 235 mg, n = 25,
- Calcium carbonate 500 mg, n = 25.

Information about the dosages and their possible variation during the course of the study are not available in the publication.

Endpoints: Serum calcium phosphate levels evaluated each month, parathormone levels and calcium levels evaluated every 6 months up to 36 months.
These endpoints were not prioritised.

Results:

After 36 months of treatment, a significant reduction was observed in the group treated with calcium acetate + magnesium carbonate versus calcium carbonate in terms of:

- phosphate levels: reduction of 0.39 mmol/l ± 0.27 versus 0.15 mmol/l ± 0.27, $p < 0.05$,
- calcium levels: reduction of 0.14 mmol/l ± 0.13 versus 0.01 mmol/l ± 0.19, $p < 0.05$.

In addition, a significant increase in magnesium levels was observed in the group treated with calcium acetate + magnesium carbonate versus calcium carbonate: increase of 0.10 mmol/l ± 0.13 versus -0.01 mmol/l ± 0.13, $p < 0.001$.

Finally, the quantity of chelating agents used in this study was significantly greater in the calcium acetate + magnesium carbonate group versus calcium carbonate in terms of:

- mean number of tablets/day: 7.92 ± 2.58 versus 6.24 ± 2.28, $p = 0.013$,
- dose of chelating agents: 2.20 ± 1.66 versus 0.60 ± 2.12, $p = 0.002$.

According to the methodology of this study (open, small patient population, no *a priori* calculation of the number of subjects needed, multiple non-prioritised efficacy endpoints, higher mean comparator dosage than that recommended by the marketing authorisation), the results of this study are exploratory, should be interpreted with caution and confirmed by studies with a better level of proof and performed on a larger number of patients.

3.2. Adverse effects

In study CALMAG-01, adverse effects were observed in 89/125 patients (71.2%) in the OSVAREN group and 95/127 (74.8%) in the RENAGEL group. The most commonly observed adverse effects were:

- musculoskeletal disorders (mainly muscle spasms): 1.7% versus 0.2%,
- gastrointestinal disorders (mainly diarrhoea and nausea): 3.6% versus 9.1%,
- metabolic disorders: 3.1% versus 1.4% with, in particular, hypermagnesemia (2.1% versus 0.5%),

3.3. Conclusion

The efficacy and tolerance of OSVAREN were evaluated in two randomised, comparative clinical studies: a phase III non-inferiority study versus RENAGEL (sevelamer) and a “supporting” study versus calcium carbonate.

After 25 weeks of treatment in 244 stable patients and aged from 18 to 85 years old, who had been on HD or HDF therapy for at least 3 months, the upper limit of the confidence interval (0.0692) was below the limit fixed in the protocol [0.15 mmol/l], thus demonstrating the non-inferiority of OSVAREN versus RENAGEL in terms of serum phosphate levels (primary efficacy endpoint).

ITT analysis confirms the observed *per protocol* results.

In the “supporting” study lead on 50 CKD and HD patients for 18 to 36 months, after 36 months of treatment a significant reduction was observed in the group treated with calcium acetate/magnesium carbonate in comparison with calcium carbonate in terms of a reduction in:

- blood phosphate level: -0.39 mmol/l ± 0.27 versus -0.15 mmol/l ± 0.27, $p < 0.05$,
- blood calcium: -0.14 mmol/l ± 0.13 versus -0.01 mmol/l ± 0 19, $p < 0.05$.

In addition, the increase in magnesium levels was larger in the group treated with calcium acetate/magnesium carbonate compared with calcium carbonate: + 0.10 mmol/l ± 0.13 versus -0.01 mmol/l ± 0.13, $p < 0.001$.
According to the methodology of this study (open, small patient population, no *a priori* calculation of the number of subjects needed, multiple non-prioritised efficacy endpoints, higher mean comparator dosage than that recommended by the marketing authorisation), the results of this study are exploratory, should be interpreted with caution and confirmed by studies with a better level of proof and performed on a larger number of patients.

In the study versus RENAGEL, the most commonly observed adverse effects with calcium acetate/magnesium carbonate were: musclar spasms (1.7% vs 0.2% with sevelamer), diarrhea (1.2% vs 1.4%) and nausea (1% vs 1.7%, metabolic disorders (3.1% vs 1.4%), and in particular hypermagnesemia (2.1% vs 0.5%).

No studies are available concerning the comparaison of the efficacy of OSVAREN versus calcium acetate (PHOSPHOSORB) or lanthanum carbonate (FOSRENOL).

In addition, it still some uncertainties about the potential long-term effects of magnesium accumulation in the bone of dialysis patients.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hyperphosphatemia, because of its bone and cardiovascular complications, may present a serious situation in patients with chronic kidney disease.

OSVAREN is intended as a preventive treatment.

The efficiency of OSVAREN has been demonstrated in term of reducing blood phosphate levels in CKD dialysis patients; the efficiency of this medicinal product in terms of its morbidity and mortality has not been established as of today .

The efficiency/tolerance ratio of this product is considered as high in this indication.

This medicinal product is a first-line therapy.

There are other alternative treatments, such as calcium carbonate, calcium acetate, sevelamer and lanthanum carbonate.

Public health benefit*:* Hyperphosphatemia is common in CKD patients, but the morbid consequences of hyperphosphatemia are not well established.

So, the burden of the disease cannot be quantified.

Reducing the impact of chronic kidney disease on quality of life is a public health need falling within the scope of an established public health priority (Public Health Act of 2004).

However, in terms of reducing hyperphosphatemia, this need is at least partially covered by existing medicines (sevelamer, other calcium salts and lanthanum salt).
From the available clinical data it is not possible to estimate the impact of OSVAREN on the morbidity and mortality associated with hyperphosphatemia in relation to comparison drugs.

Moreover, there is some uncertainties about the tolerance of OSVAREN in terms of the accumulation of magnesium in the tissues (in particular bone tissue).

Consequently, taking into account existing treatments, it is not expected any public health benefit from OSVAREN in this indication.

The actual benefit of OSVAREN is substantial.

4.2. Improvement in actual benefit (IAB)

OSVAREN, a combination of calcium acetate and magnesium carbonate, does not offer any improvement in actual benefit (IAB V) in the treatment of hyperphosphatemia in CKD and HD or peritoneal dialysis patients.

4.3. Therapeutic use

In CKD and dialysis patients, hyperphosphatemia is associated with a heightened risk of morbidity (Block, 1998 and 2000), mainy bone and cardiovascular morbidity.

Despite taken measures to monitor serum phosphate levels through diet and by dialysis, these patients most often need to use phosphate binding drugs. In this situation, calcium salts, sevelamer or lanthanum carbonate are used.
OSVAREN represents an alternative to the other phosphate chelating agents in cases of hyperphosphatemia combined with CKD treated by haemodialysis or peritoneal dialysis.

4.4. Target population

The target population of OSVAREN is CKD patients on dialysis with hyperphosphatemia.

The number of CKD patients on haemodialysis or peritoneal dialysis is estimated to be around 31,000 (Report by REIN 2007[3]) in France.
According to experts, between 70% and 95% of these patients would have hyperphosphatemia requiring treatment by Phosphate binders, i.e. between 20,000 and 30,000 patients.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosages in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

[3] Réseau Epidémiologie et Information en Néphrologie [Nephrology Epidemiology and Information Network], http://www.soc-nephrologie.org/REIN/index.htm