HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

11 June 2008

RENAGEL 400 mg, film-coated tablet:
Pack of 360. CIP code: 357 264-2

RENAGEL 800 mg, film-coated tablet:
Pack of 180. CIP code: 357 265-9

Applicant: GENZYME SAS

Sevelamer

List I

Date of Marketing Authorisation (centralised): 23 April 2001
Date of MA variation (extension): 1 June 2007

Reason for request: 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 new indication: “RENAGEL is indicated for the control of hyperphosphataemia in adult patients receiving ***peritoneal dialysis***”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
sevelamer

1.2. Indication
RENAGEL is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis ***or peritoneal dialysis.***

RENAGEL 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.

1.3. Dosage
Children: Safety and efficacy of this product have not been established in children under the age of 18 years.

Adults and elderly (> 65 years): For patients who are not on phosphate binders, dosage is determined individually according to serum phosphate concentrations as indicated in the table below:

Serum phosphate levels in patients not on phosphate binders	Starting dose of RENAGEL
1.76 – 2.42 mmol/l	Two 400-mg tablets 3 times daily or one 800-mg tablet 3 times daily
2.42 – 2.91 mmol/l	Three 400-mg tablets 3 times daily or two 800-mg tablets 3 times daily
> 2.91 mmol/l	Four 400-mg tablets 3 times daily or two 800-mg tablets 3 times daily

The dose range may vary between one and five 800-mg tablets per meal (or between one and ten 400-mg tablets per meal). The mean dose administered during clinical studies was 4 capsules per meal which is equivalent to two 800-mg tablets per meal (or four 400-mg tablets per meal).

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2007 Classification:
V : various
V03 : all other therapeutic products
V03A : all other therapeutic products
V03AE : drugs for treatment of hyperkalaemia and hyperphosphataemia
V03AE02 : sevelamer

2.2. Medicines in the same pharmacotherapeutic class:
Lanthane carbonate:
FOSRENOL (250, 500, 750 and 1000 mg), chewable tablets.

2.3. Medicines with a similar therapeutic aim
Aluminum salt (aluminum hydroxide/carbonate gel):
LITHIAGEL oral suspension in bottles

Calcium binders (calcium carbonate):
- CALCIDIA 1.54 g, granules for oral suspension in sachets
- EUCALCIC 1.2 g/15 ml, oral suspension in sachets

NB: calcium acetate (comparator used in the study submitted in the dossier) is not marketed in France.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of the efficacy and safety of RENAGEL in this extension of indication in patients receiving peritoneal dialysis is based on a phase III clinical study (study REN00304, unpublished).

Objective: to compare the efficacy and safety of RENAGEL (sevelamer) and calcium acetate in terms of changes in serum phosphorus levels in patients receiving peritoneal dialysis.

Method: open-label, randomised, non-inferiority study versus calcium acetate (not marketed in France), in 143 patients (RENAGEL group: n = 97; calcium acetate group: n = 46) receiving peritoneal dialysis and followed up for 12 weeks.

Non-inferiority was accepted if the upper limit of the confidence interval of the difference in the change in plasma phosphate levels did not exceed a limit fixed at 0.94 mg/dl (0.3 mmol/l). The analysis was conducted *per protocol*.

Inclusion criteria: patients with chronic renal failure receiving peritoneal dialysis for 8 weeks or more with:
- plasma phosphate levels above 5.5 mg/dl (1.77 mmol/l) after a 2-week period without phosphate binder treatment,
- normal serum calcium levels (between 8.40 and 10.40 mg/dl [2.10-2.60 mmol/l]) after a 2-week period without phosphate binder treatment.

Treatment:
After 2 weeks without treatment, all the patients were randomly assigned to two groups according to a 2:1 ratio:
- RENAGEL 2 x 800 mg, 3 times daily (n=97),
- Calcium acetate 538 mg, 3 times daily (n=46).

Primary efficacy endpoint: Change in plasma phosphate levels relative to baseline after 12 weeks of treatment.

RESULTS:
Baseline patient characteristics were similar in both groups.

Change in serum phosphors levels relative to baseline (mg/dl) at 12 weeks.

	RENAGEL mean [95% CI]	Calcium acetate mean [95% CI]	Mean difference 95% CI (upper margin of CI)	p
PP Analysis	N=72 -1.612 [-1.62 ; -1.6]	N=31 -1.809 [-1.83 ; -1.79]	0.197 (0.741)	<0.001
ITT Analysis	N=95 -1.586 [-1.59 ; -1.58]	N=44 -1.630 [-1.65 ; -1.62]	0.045 (0.514)	<0.001

After 12 weeks of treatment, the upper limit of the confidence interval of the observed difference was 0.741 mg/dl, i.e. below the limit fixed in the protocol (0.94 mg/dl). The non-inferiority of RENAGEL compared to calcium acetate was demonstrated.
The ITT results confirmed the results of the *per protocol* analysis.

3.2. Adverse effects

During this study, 107 adverse events were observed: 80 in the 35 patients (36.1%) treated by RENAGEL and 27 in the 16 patients (34.8%) treated by calcium acetate.

The severity of the adverse events was generally mild to moderate.

The most frequently observed adverse reactions with RENAGEL were gastrointestinal disorders: 26.8% with RENAGEL [dyspepsia (12.4%), diarrhoea (5.2%), nausea (5.2%)] versus 13% with calcium acetate.

The most frequently observed adverse event with calcium acetate was hypercalcaemia: 10.9% with calcium acetate versus 0% with RENAGEL.

In this study, peritonitis (serious adverse event) was observed in eight patients with RENAGEL and two patients with calcium acetate.

These adverse reactions are similar to those observed during RENAGEL treatment in haemodialysed patients; no specific adverse reaction in the therapeutic indication of patients receiving peritoneal dialysis was identified.

3.3. Conclusion

In study REN00304, the efficacy and safety of RENAGEL were evaluated in patients receiving peritoneal dialysis.

After 12 weeks of treatment, the upper limit of the confidence interval of the observed difference was 0.741 mg/dl, i.e. below the limit fixed in the protocol (0.94 mg/dl). The non-inferiority of RENAGEL compared to calcium acetate was demonstrated. The administration of RENAGEL 2 x 800 mg 3 times daily caused a mean reduction in plasma phosphate levels of 1.612 mg/dl (cf. table 1).

In general the severity of the adverse events observed during this study was mild to moderate. The adverse reactions most frequently reported with RENAGEL were gastrointestinal disorders: dyspepsia, diarrhoea and nausea.
According to the SPC, no data are available about the effect of RENAGEL treatment on the bone.

No comparative data versus lanthane carbonate (FOSRENOL) are currently available.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hyperphosphataemia may be a serious condition in chronic renal failure patients, in particular because of its bone and cardiovascular complications.

The proprietary medicines RENAGEL are intended for preventive treatment.
The efficacy/safety ratio of these products is high in this indication.
These products are used for first-line therapy.
There are alternative treatments including, in particular, calcium binders and lanthane carbonate.

> Public Health Benefit:
> Hyperphosphataemia frequently occurs in chronic kidney failure patients. However, as the morbidity due to this hyperphosphataemia is poorly defined, the burden of the disease cannot be quantified.
> The therapeutic need is at least partially covered by existing medicinal products (FOSRENOL and calcium salts).
> It is impossible to assess the impact of RENAGEL on hyperphosphataemia-related morbidity and mortality relative to comparator products from the available clinical data.
> Consequently, taking into account the existing treatments, RENAGEL is not expected to benefit public health.

The actual benefit of RENAGEL is substantial in this extension of indication.

4.2. Improvement in actual benefit

In the extension of indication in patients receiving peritoneal dialysis, RENAGEL does not improve the actual benefit (IAB V) of therapeutic use.

4.3. Therapeutic use

In dialysed chronic renal failure patients, hyperphosphataemia is associated with an increased risk of morbidity (Block, 1998 and 2000), in particular due to bone and cardiovascular disease.

Despite the institution of measures to control serum phosphate levels by diet and dialysis, these patients usually have to take phosphate binders. In this setting, patients may benefit from treatments such as calcium salts, sevelamer, or lanthanum carbonate.

4.4. Target Population

The number of patients with chronic renal failure receiving haemodialysis or peritoneal dialysis may be estimated to be approximately 31,000 in France.
According to the experts, between 70% and 95% of these patients have hyperphosphataemia requiring therapeutic management, i.e. between 20,000 and 30,000 patients.

The annual report of the French registry of renal replacement therapy for chronic renal failure (REIN 2005, Biomedecine Agency), considers that 8% of the total population of dialysed patients receive peritoneal dialysis.

The number of patients receiving peritoneal dialysis is therefore between 1600 and 2400 patients.

On this basis, the target population of RENAGEL in patients receiving peritoneal dialysis may be estimated to be between 1600 and 2400 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for hospital use and various public services in the marketing authorisation's extension of indication and dosages.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%