



European Medicines Agency

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Product Name : **Renagel**

Procedure No: **EMEA/H/C/000254/II/56**

SCIENTIFIC DISCUSSION

1. Introduction

Renagel (sevelamer), a non-absorbed, calcium and metal-free phosphate binder, was authorised in Europe under centralised procedure on 28 January 2000 for the indication of

“control of hyperphosphatemia in adult patients on haemodialysis (HD) Renagel should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25 – dihydroxy Vitamin D₃ or one of its analogues to control the development of renal bone disease”

and is currently marketed in most EU countries and worldwide. Renagel was authorised under exceptional circumstances but this was lifted recently (Commission Decision 26 June 2006) following fulfilment of all specific obligations by the MAH.

The MAH applied for this Type II variation (EMA/H/C/254/II/56) to extend the indication to patients on *peritoneal dialysis (PD)*. The application is supported by a clinical study in patients receiving peritoneal dialysis (study REN00304) and relevant literature.

2 Clinical aspects

The data presented by the MAH reviews the benefit/risk profile of Renagel in patients on peritoneal dialysis (PD) taking into account protocol REN00304 PD study and relevant efficacy and safety data available since the marketing authorisation.

The study REN00304 compared the effects of dosed three times daily with meals and calcium acetate on serum phosphorus control in peritoneal dialysis patients, and evaluated the safety and tolerability of in this population. The results demonstrated non inferiority of compared to calcium acetate in terms of reduction from baseline in serum phosphorus level. The study also confirmed the safety profile that was similar to that already established in the haemodialysis population.

The clinical trial was performed in accordance with GCP, as stated by the MAH.

As patients with late chronic kidney disease (CKD) stage 5 have minimal or no residual renal function, the excretory function of the kidney must be substituted via dialysis, either haemodialysis or peritoneal dialysis. The approach to treatment of hyperphosphataemia for both dialysis modalities is essentially the same. As renal failure progresses, the glomerular filtration rate (GFR) falls and renal excretion of phosphorus is no longer sufficient to maintain normal serum phosphorus levels in the face of continuing absorption of phosphorus from the gastrointestinal tract and mobilization of phosphorus from bone. Consequently, hyperphosphataemia develops, usually in association with low levels of calcitriol and worsening hyperparathyroidism. Hyperphosphataemia is associated also with increased renal bone disease (renal osteodystrophy), increased cardiovascular and other soft tissue calcification and increased mortality.

Dietary phosphate restriction and/or dialysis are usually insufficient to adequately control serum phosphorus. Therefore, phosphate binders are used by almost all dialysis patients to decrease intestinal absorption of phosphate to the point that dialytic clearance can maintain an acceptable serum phosphorus concentration ideally between 1.13 - 1.77 mmol/l for stage 5 adult patients.

Peritoneal dialysis is one of two dialysis modalities to treat chronic uraemic patients. Haemodialysis is used more extensively than peritoneal dialysis, but there is a wide variation in practice across different countries. Coagulation abnormalities, lipid abnormalities and fluid overload are commonly felt to be more common in peritoneal dialysis patients although new onset cardiovascular disease is seen similar rate in both modalities. Comparable outcomes have been reported over the last 10 years.

The phosphate binders currently available contain mainly calcium or sometimes aluminium, which are associated with a variety of undesirable effects. Sevelamer hydrochloride, a non-absorbable phosphate-binding polymer, was synthesised to enhance phosphorus excretion while minimising

systemic effects observed with other phosphorus binders. There are also some evidence that may have beneficial effect on a number of plasma biomarkers (C-reactive protein (CRP), uric acid, bone specific alkaline phosphatase, random blood glucose and glycosylated haemoglobin).

2.1 Clinical efficacy

Main study (REN00304)

The MAH presented one clinical study, protocol REN00304. The objective of this study was to evaluate the safety and efficacy of sevelamer hydrochloride compared with calcium acetate in peritoneal dialysis patients.

The study was a phase 3, multicentre, open label, and randomised, parallel group study. A total of 15 investigators from 17 investigative sites in Belgium, Denmark, France, Italy, Spain, The Netherlands, and United Kingdom participated in this study. The first patient was enrolled in December 2004 and the last patient completed in March 2006. Calcium acetate was used as the control group.

Study population

A total of 150 patients were planned for randomisation. Main criteria for inclusion were chronic kidney disease (CKD) and peritoneal dialysis (Continuous Ambulatory (CAPD), Ambulatory (APD), or Continuous cyclical (CCPD)) for 8 weeks or longer and serum phosphorus level > 5.50 mg/dL (1.77 mmol/L) after two weeks washout from patient's usual phosphate binder.

Methods

i. Study objectives

Primary objectives in peritoneal dialysis patients were to compare the effects of sevelamer dosed three times per day (TID) and calcium acetate dosed TID on serum phosphorus, and to investigate the safety and tolerability of sevelamer.

Secondary objectives were to compare the effects of sevelamer TID and calcium acetate on serum calcium-phosphorous product (CaxPO₄), serum lipids (total cholesterol, LDL cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides) and a number of plasma biomarkers (random blood glucose, HbA1C, BSAP, uric acid and CRP).

ii. Study endpoints

The primary efficacy endpoint was serum phosphorus level – a target of non-inferiority in comparison with calcium acetate was used as the criterion for power calculations. Non-inferiority was defined as a difference in the serum phosphorus change between treatment groups of statistically significantly less than 0.3 mmol/L.

Secondary efficacy endpoints were change in serum calcium-phosphorus product (CaxPO₄) level, change in total cholesterol, LDL cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides, and change in random blood glucose, glycosylated haemoglobin (HbA1C), bone specific alkaline phosphatase (BSAP), uric acid, and C-reactive protein (CRP).

Safety endpoints included incidence of adverse events (AEs) and serious adverse events (SAEs), changes in vital signs, number of hypercalcaemic episodes and changes in clinical laboratory evaluations (serum phosphorous, serum calcium (albumin-adjusted), calcium phosphorous product, intact parathyroid hormone (iPTH), lipids, CRP, uric acid, bone-specific alkaline phosphatase (BSAP), glucose, HbA1C, FBC, blood urea nitrogen, sodium, potassium, chloride, bicarbonate).

iii Statistical analysis

The primary endpoint efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 12/Final among the Per-Protocol Set. A Full Analysis Set (FAS) analysis was performed as a confirmatory analysis.

The secondary endpoint efficacy analysis was an assessment of the change from baseline at Week 12/Final in the following parameters was analysed: total cholesterol, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, calcium phosphorus product, and plasma biomarkers (CRP, uric acid, bone-specific alkaline phosphatase (BSAP), HbA1C, random blood glucose).

Comparisons between treatment groups were assessed using a two-sided Wilcoxon rank sum test and changes within treatment groups was assessed using Wilcoxon Signed Rank test. All these analyses were tested at the $\alpha = 0.05$ (2-tailed) level of significance unless otherwise specified. p-values <0.05 were considered statistically significant.

All treatment emergent AEs (TAEs)/SAEs and those related to study treatment were summarised and tabulated by treatment group for each system organ class and preferred term.

iv. Study Population

A total of 253 patients were screened for this study, 143 of whom were randomised to sevelamer (n=97) or calcium (n=46) in a 2:1 ratio following the washout period (safety set). The full analysis set (FAS) consisted of 139 patients who received study medication and had at least one post-baseline serum phosphorus assessment (sevelamer, n=95; calcium, n=44). Thirty-six patients were excluded from the Per Protocol set, which consisted of 103 patients (sevelamer, n=72; calcium, n=31). The main reasons for exclusion were poor compliance ($<70\%$) (sevelamer, n=15, calcium, n=10) and less than 3 weeks on treatment (sevelamer, n=7, calcium, n=3). The study was completed by 76% of patients in the sevelamer group (n=74) and 65% of patients in the calcium group (n=30). AEs were the main reason for premature withdrawal from the study (18% of sevelamer-treated patients and 28% of calcium-treated patients).

Results

Patient exposure and Demographics

A total of 253 patients were enrolled. 110 patients failed screening or washout. 143 patients were randomised to study treatment in a 2:1 fashion: 97 patients received sevelamer hydrochloride (SG) and 46 patients received calcium acetate (CG).

Of the 143 patients in the Safety Set (93 male, 50 female) the mean age was 54.4 years (range 19 to 91 years). Most patients were Caucasian (90%), with Blacks (2%), and Asians (5%) and Others (3%) comprising the remainder. 10% were smokers, 22% had diabetes and 84% reported hypertension at baseline. Baseline characteristics did not differ between the groups. All patients were on a phosphate-binder before study entry. Concomitant medication was similar in both groups.

The study was completed by 104 patients, while 39 patients discontinued the study because of following reasons: adverse event (30), non-compliance (1), withdrew consent (1), other reasons (7).

Efficacy

The primary efficacy endpoint was analysed in the Per Protocol Set. The mean serum phosphorus content at baseline was 7.48 mg/dL (2.40 mmol/L) in the sevelamer group and 7.29 mg/dL (2.34 mmol/L) in the calcium group. At week 12/final the values were 5.86 mg/dL (1.88 mmol/L) in the sevelamer group and 5.48 mg/dL (1.76 mmol/L) in the calcium group, which represented statistically significant change ($p<0.001$) from baseline of -1.61 mg/dL (-0.52 mmol/L) and -1.81 mg/dL (-0.58 mmol/L), respectively. The difference in mean change (difference=sevelamer-

calcium) was 0.197 mg/dL (0.061 mmol/L) with an upper 97.5% confidence bound of 0.741 mg/dL (0.237 mmol/L) thus establishing non-inferiority margin of 0.929 mg/dL (0.3 mmol/L). The Full Analysis Set results were comparable.

There was a statistically significant decrease ($p < 0.001$) from baseline to week 12/final in both treatment groups for Calcium-Phosphorous product. There was no statistically significant difference between the sevelamer and calcium treatment groups at any time point for this variable.

A statistically significant decrease ($p < 0.001$) from baseline to week 12/final for total-, LDL-, and non-HDL cholesterol was observed in the sevelamer group, but not in the calcium group (full analysis set). These changes were statistically significant between treatment groups ($p < 0.001$). For tryglycerides there was a statistically significant increase in terms of percentage change from baseline to week 12/final in both the sevelamer and calcium groups.

The CHMP concluded that treatment for 12 weeks with sevelamer hydrochloride was non-inferior to 12 weeks treatment with calcium acetate (calcium) in reducing serum phosphorus levels. The serum phosphorus concentrations in both groups reached the K/DOQI (Kidney Disease Outcomes Quality Initiative guidelines, 2003) target concentration in approximately half the patients. The magnitudes of reduction in serum phosphorus were similar to studies conducted in the HD population.

The mean changes in serum parameters are given in Table 1 below.

Table 1. Mean changes in serum parameters after 12 weeks of treatment with sevelamer or calcium acetate (full analysis set)

	sevelamer (n 95)			calcium (n 44)			Between groups
Serum parameter	Baseline	Week 12/final	Change	Baseline	Week 12/final	Change	p-value
Phosphorus (mg/dL)	7.48	5.86	-1.61±1.16*	7.29	5.48	-1.81±1.52*	ND
Ca x P product (mg ² dL ²)	71.1	56.1	-15±12.1*	70.9	57.3	-13.6±15.5*	0.306
Calcium (albumin-adjusted) (mg/dL)	9.54	9.59	0.05	9.58	10.04	0.46*	0.006
Intact parathyroid hormone (pgl/mL)	398	340	-44**	512	328	-87**	0.247
Total cholesterol (mg/dL)	183.5	152.2	-15.20%*	180.2	180.1	0.96%	<0.001
LDL-cholesterol (mg/dL)	120.6	90.0	-23.15%*	118.5	117.1	0.27%	<0.001
HDL-cholesterol (mg/dL)	46.8	46.7	0.72%	42.5	42.1	-1.17%	0.529
Non-HDL-cholesterol (mg/dL)	136.8	105.5	-19.69*	137.6	138.0	2.23%	<0.001
Triglycerides (mg/dL)	155.6	162.6	17.76%	173.1	197.2	21.38%**	0.410
Uric acid (mg/dL)	6.46	5.90	-0.54*	6.20	6.19	-0.01	0.001
C-reactive protein (mg/dL)	12.99	18.99	-0.75	13.86	15.53	-2.57	
Random blood glucose (mg/dL)	107.4	109.1	3.7	113.0	114.9	0.4	
HbA1c (%)	5.76	5.77		6.22	6.20		
BSAP (ug/L)	12.32	16.66	3.68*	15.58	17.15		

*p<0.001 **P<0.05. All values means except iPTH (medium). All data from full analysis set, except serum phosphorus (per protocol set, Sevelamer group N=75, Calcium group N=31). ND=not determined

Lipid abnormalities are common in peritoneal dialysis patients. A statistically significant decrease (p< 0.001) from baseline for total-, LDL-, and non-HDL cholesterol was observed in the sevelamer group and may favour additional benefit in these patients. The changes in lipids were not seen in the calcium group.

Clinical studies in special populations

A sub-group analysis for the primary efficacy endpoint was performed separately within the anuric and non-anuric patients.

These results were similar to those seen in total patient sample. Both treatments resulted in statistically significant decrease in serum calcium-phosphorus product from baseline to week-12/final.

2.2 Clinical safety

Patient exposure

Patients received sevelamer for an average of 10.0 weeks (SG 10.3 weeks; CG 9.4 weeks; $p=0.236$). The median percentage compliance in the Safety Set was similar in both groups, 91.3% in the SG and 88.5% in the CG. In the Safety Set the number of patients evaluated was 97 in the SG and 46 in the CG, a 2:1 ratio giving an exposure of approximately 7000 patient days for sevelamer and 3000 patient days for calcium.

Adverse events (AEs)

A total of 317 treatment-emergent AEs (TAEs) occurred in 108 patients during randomised treatment period. A similar percentage of patients experienced TAEs in the two treatment groups: 75 patients (77.3%) in the sevelamer group ($n=97$) experienced 240 adverse events, and 33 patients (71.7%) in the calcium group ($n=46$) experienced 77 adverse events. The highest frequency of TAEs for both treatment groups were gastrointestinal disorders with statistically significant higher number in the sevelamer group ($p = 0.003$). Most of the AEs were mild to moderate in intensity.

Table 2. Frequency of treatment-emergent adverse events.

Parameter	Total	sevelamer n (%)	calcium n (%)	p-value
Patients	143	97 (100)	46 (100)	
Treatment-Emergent AEs	108	75 (77.3)	33 (71.7)	0.534
Treatment-Related AEs	51	35 (36.1)	16 (34.8)	1.000
AEs resulting in discontinuation	30	17 (18)	13 (28)	
Serious AEs (SAEs)	24	19 (19.6)	5 (10.9)	0.236
Severe AEs	24	14 (14.4)	10 (21.7)	
Deaths	2	1 (1.0)	1 (2.2)	

A total of 107 events were considered treatment related: 80 events in 35 patients (36.1%) in the sevelamer group and 27 events in 16 patients (34.8%) in the calcium group. The most frequently occurring treatment related adverse event in the sevelamer group was dyspepsia (14 events in 12 patients, 12.4%).

Thirty patients, 17/97 patients (18%) in the sevelamer group and 13/46 (28%) in the calcium group discontinued the study due to AEs. In 8 cases (4 patients in each group) the reason was renal transplantation.

Table 3. Treatment-Emergent adverse events in > 1 patient per group assessed as related to study treatment (Safety Set)

MedDRA SOC/ Preferred Term	sevelamer (N97) Patients N(%)	Events N	calcium (N46) Patients N(%)	Events N	p-value
Any Adverse Event	35(36.1%)	80	16 (34.8%)	27	1.000
Gastrointestinal disorder	26 (26.8%)	42	6 (13.0%)	7	0.086
Abdominal distension	3 (3.1%)	4	0	0	0.551
Abdominal pain upper	1 (1.0%)	2	1 (2.2%)	1	0.541
Constipation	4 (4.1%)	4	1 (2.2%)	1	1.000
Diarrhoea	5 (5.2%)	8	1 (2.2%)	1	0.664
Dyspepsia	12 (12.4%)	14	3 (6.5%)	3	0.387
Nausea	5 (5.2%)	5	1(2.2%)	1	0.664
Vomiting	3 (3.1%)	4	0	0	0.551
General disorders and administration site conditions	5 (5.2%)	6	0	0	0.176
Fatigue	3 (3.1%)	3	0	0	0.551
Investigations	2 (2.1%)	8	5 (10.9%)	8	0.035
Blood calcium increased	1 (1.0%)	2	3 (6.5%)	4	0.098
Blood parathyroid hormone increased	2 (2.1%)	2	2 (4.3%)	2	0.594
Calcium phosphate product increased	1 (1.0%)	1	2 (4.3%)	2	0.242
Metabolism and nutrition disorders	6 (6.2%)	7	5 (10.9%)	5	0.332
Anorexia	3 (3.1%)	3	0	0	0.551
Dehydration	1(1.0%)	2	0	0	1.000
Hypercalcaemia	0	0	5 (10.9%)	5	0.003
Musculoskeletal and Connective tissue disorders	5 (5.2%)	6	2 (4.3%)	3	1.000
Arthralgia	3 (3.1%)	3	1 (2.2%)	1	1.000
Pain in extremity	1 (1.0%)	1	1 (2.2%)	1	0.541
Nervous system disorders	2 (2.1%)	2	0	0	1.000
Skin and subcutaneous tissue disorders	4 (4.1%)	4	4 (8.7%)	4	0.270
Pruritus	4 (4.1%)	4	3 (6.5%)	3	0.681

There were 15 episodes of peritonitis reported in patients randomised to the study. Four (4) peritonitis episodes were reported as AEs and 11 as SAEs. The sevelamer hydrochloride group experienced 11

episodes (8 SAEs and 3AEs). The calcium acetate group experienced 2 cases (2 SAEs). Two (2) peritonitis episodes occurred during the washout period (1 SAE, 1 AE).

The higher number of peritonitis episodes in the Renagel treated group compared with the calcium acetate treated group remains a matter for further surveillance. At present there is no evidence of an association between Renagel use and peritonitis or any related factor in this small group of patients with peritonitis to fully explain a difference in number of cases between the two arms of the study. For that reason the MAH agree in providing prospective data on the occurrence of peritonitis.

Taking also into account that one of the peritonitis infected patient, was taking immunosuppressive drugs (tacrolimus) and also that 17 % of the patients included in the REN00304 study had previous renal transplantation, with at least two patients still on immunosuppressive drugs, the interaction with immunosuppressive medicinal products should be highlighted. In addition during the assessment no final conclusion could be drawn to the drug-drug interactions between sevelamer hydrochloride and anti-arrhythmics/anti-epileptics from the results of the REN00304 study. The MAH therefore proposed that instructions for intake of these drugs should be given in the SPC and in the Package Leaflet.

Serious adverse events(SAEs) and deaths

During the study 31 SAEs occurred in 24 patients; 26 SAEs for 19 patients (19.6%) in the sevelamer group and 5 SAEs for 5 patients (10.9%) in the calcium group. The most frequently occurring treatment-emergent SAE was peritonitis (8 events in 8 patients in the sevelamer group and 2 events in 2 patients in the calcium group). Six AEs of severe intensity occurred in 2 patients in the sevelamer group and 6 events occurring in 3 patients in the calcium group were considered related to study drug.

Two patients died during the study. Both deaths were assessed as not related to study drug by the investigator. One patient in the calcium group died in a road traffic accident 11 days after starting study drug. One patient in the sevelamer group died of unknown reason 6 weeks after starting study drug. An autopsy was not performed and the cause of death remained unknown. Cardiac arrest was suspected.

The CHMP considered that the number of adverse events and the number of patients who had AEs differ between the study groups. AEs which were considered treatment related differ between the groups. A higher percentage of patients on sevelamer experienced gastrointestinal treatment-related events, which is consistent with results from previous studies with sevelamer. However, in this study the difference did not reach statistical significance.

Laboratory findings

There was a significant decrease from baseline in bicarbonate level with sevelamer (from 22.1 mmol/L at baseline to 21.3 mmol/L at 12 weeks; $p=0.003$) and a significant difference in mean change between treatment groups ($p=0.008$). However, the change in bicarbonate in the sevelamer group was not considered to be clinically significant and metabolic acidosis was reported in just one sevelamer treated patient. The worsening of metabolic acidosis is already mentioned in the SPC section 4.4 for haemodialysis patients. The MAH was requested to discuss if there was a need for additional risk minimisation measures for the peritoneal dialysis patients.

Hypercalcaemia (i.e. albumin-adjusted serum calcium ≥ 11.0 mg/dL) was experienced by significant more patients in the calcium group compared with the sevelamer group ($p=0.001$). Patients on calcium had a higher frequency of hypercalcaemia, increased blood calcium, and increased calcium phosphorus product. These events may be risk factors for development of tissue calcifications.

Safety in special populations

A sub-group analysis for the primary efficacy endpoint was performed separately within the anuric (N 27) and non-anuric (N 112) patients. The safety results were similar to those seen in total patient sample.

There were not data in this clinical trial in pregnant or lactating women, patients with hepatic impairment or cardiac impairment, immunocompromised patients and populations with genetic polymorphism will be provided if applicable. The MAH is committing to provide a safety summary of the complete clinical trials and post authorisation data for Renagel to date in the haemodialysis and peritoneal dialysis indications.

3 Pharmacovigilance

3.1 Risk Management Plan

A Risk Management Plan (RMP) was not submitted with the initial variation application but it was requested with the Request for Supplementary Information in November 2006. The MAH has then provided a Risk Management Plan which was assessed.

The current Renagel SPC reflects this established safety profile and covers all important risks identified until now. The important unidentified potential risks captured as adverse effects which will be additionally observed in patients treated with Renagel can be evaluated in the context of established Pharmacovigilance practice. The main new issues identified are relevant to reported cases of peritonitis and as well as the functioning of the current surveillance systems.

In the revised RMP the MAH should provide a summary table of planned pharmacovigilance actions for each safety concern. Where no action beyond routine pharmacovigilance is planned, it should be fully justified. The evaluation of the need for risk minimisation activities should list all safety concerns with discussions whether routine (i.e. changes to the Product Information) risk minimisation activities will be sufficient or whether additional risk minimisation activities (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes) will be required.

Identified and potential risks including gastrointestinal ADRs such as intestinal obstruction, and ileus, vitamin deficiency, increased serum chloride levels, worsening of acidosis, hypothyroidism should be discussed in the revised RMP. Whether these risks are similar in HD and PD patients should also be discussed.

In the updated RMP requested by the CHMP the MAH has agreed to revise the Pharmacovigilance Plan and re-evaluate the Need for Risk Minimisation Activities.

More specifically there will be increased monitoring of peritonitis and provision of additional information material for patients and health care professionals including risk factors and precautions against infection. The MAH will review the collected data from the prospective registry and they will update the RMP based on the review. In addition there will be evaluation of the need for risk minimisation activities and any planned pharmacovigilance actions for any safety concerns.

The details of important identified and potential risks including gastrointestinal ADRs such as intestinal obstruction, and ileus, vitamin deficiency, increased serum chloride levels, worsening of acidosis, hypothyroidism will be discussed including clarification on whether these risks are similar in HD and PD patients which will also be submitted.

The discussion on co-morbidities such as diabetes, hypertension, hyperlipidemia, heart failure, and chronic lung diseases will be added and as well as the epidemiology of identified or potential risks in the target population will be studied.

The ongoing safety concerns will be closely monitored and information on special patient groups, important missing information, and the impact of identified and potential risk of Renagel will be added. In addition the present off-label use will be estimated and provided.

4 Overall Scientific Discussion and Benefit/Risk Assessment

In kidney failure patients, when GFR drops below 25% of normal, compensatory increases in renal excretion are no longer sufficient to maintain normal serum phosphorus level. Control of serum phosphorus is critical to prevent metastatic calcification, a condition where calcium and phosphate precipitate into soft tissues, often in association with a high calcium phosphorus product. Elevated serum phosphorus and calcium phosphorus product are associated with increased risk of death in dialysis patients.

Patients with chronic kidney disease on dialysis are usually placed on phosphorus-restricted diets in attempt to control serum phosphorus levels. Dietary phosphorus restriction is usually insufficient to control serum phosphorus levels, and phosphate binders are also used to decrease absorption of dietary phosphorus. Sevelamer (Renagel) is a non absorbable phosphate-binding polymer, approved for the control of serum phosphorus in adult patients on haemodialysis.

The MAH has now conducted one clinical study, protocol REN00304 in peritoneal dialysis patients. The objective of this study was to evaluate the safety and efficacy of sevelamer hydrochloride compared with calcium acetate in peritoneal dialysis patients.

Regarding the efficacy, it is concluded that treatment for 12 weeks with sevelamer hydrochloride was non-inferior to the 12-week treatment with calcium acetate (calcium) in reducing serum phosphorus levels. The serum phosphorus concentrations in both groups reached the K/DOQI guideline target concentration in approximately half the patients. The magnitudes of reduction in serum phosphorus were similar to studies conducted in the HD population.

Regarding the safety of the product, the clinical trial REN00304 conducted with Renagel in the PD population has shown that the product is well tolerated in general in this population. The safety profile of Renagel in this new population is consistent with patients' underlying renal disease and with the known safety profile for Renagel. No newly important and potential risks have been identified in this population. Although a higher percentage of patients on sevelamer experienced gastrointestinal events, that is consistent with results from previous studies with the product. The higher prevalence of peritonitis in the Renagel treated group compared with the calcium-acetate treated group and compared with reported prevalence of peritonitis episodes in the literature remains a matter for further surveillance. At present there is no evidence of an association between Renagel use and peritonitis. Therefore, the MAH has proposed modifications to the original risk minimization strategy to follow up the reported cases by the collection of additional information at sites and provide it in the PSURs every six months for the period of two years after approval of this variation.

Because failure of a transplant kidney is an increasing reason for end-stage renal disease necessitating dialysis, the CHMP proposed that the interactions with tacrolimus should also be indicated in the Summary of Product Characteristics (SPC). In addition, cyclosporine A, tacrolimus and mycophenolate mofetil should be mentioned also in the Package Leaflet because up to 50 % of patients still continue to take immunosuppressive drugs to maintain residual renal function when on dialysis.

The CHMP suggested that drug-drug interactions between sevelamer hydrochloride and anti-arrhythmics/anti-epileptics could not be accurately judged from the results of the REN00304 study. Therefore instructions for intake of these drugs should be given in the SPC and in the Package Leaflet.

The Risk Management Plan will be revised and re-submitted to the CHMP for evaluation. The MAH has accepted this commitment.

The CHMP concluded that the overall benefit-risk is favourable for the control of hyperphosphatemia in adult patients receiving peritoneal dialysis and agreed to the extension of the indication of Renagel as applied by the MAH