SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Renagel. This scientific discussion has been updated until 1 March 2003. For information on changes after this date, please refer to module 8B.

1. Introduction

Hyperphosphataemia is common in patients with end-stage renal failure (ESRF) and may be associated with debilitating sequelae.

Treatment of hyperphosphataemia consists of dietary phosphorus restriction and/or dialysis and phosphate binders. Almost all dialysis patients require phosphate binders (calcium acetate, calcium carbonate, aluminium hydroxide). The use of calcium-based phosphate binders can result in chronic calcium overload, hypercalcemia and soft tissue calcification. Hypercalcemia is particularly common in patients treated with calcitriol and other vitamin D analogues. Aluminium-based phosphate binders are associated with significant toxicity due to small amounts of absorbed aluminium (encephalopathy, osteomalacia, myopathy).

Sevelamer is a non-absorbed phosphate binding poly (allylamine hydrochloride) polymer, free of aluminium and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate ions through ionic and hydrogen bonding. By binding phosphate in the gastrointestinal tract, sevelamer lowers the phosphate concentration in the serum. Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone, probably because the product itself does not contain calcium.

Renagel capsules are indicated for the control of hyperphosphatemia in adult haemodialysis patients. 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.

The dosage of sevelamer is determined individually based on serum phosphate concentration. If Renagel is prescribed as an alternative phosphate binder, Renagel should be given in equivalent doses on a mg weight basis compared to the patient's previous calcium based phosphate binder. Serum phosphate levels should be closely monitored and the dose of Renagel adjusted accordingly with the goal of lowering serum phosphate to 1.94 mmol/l or less. Serum phosphate should be tested every one to three weeks until a stable serum phosphate level is reached and on a regular basis thereafter. The dose range may vary between 1 and 10 capsules per day.

2. Chemical and pharmaceutical aspects

Renagel hard capsules:

Composition

Renagel is presented as white opaque hard gelatin capsules containing 403 mg of sevelamer as active ingredient and silica, colloidal anhydrous and stearic acid as excipients. The capsules are imprinted with the identification code G403. The primary packaging material is composed of high density polyethylene bottles (HDPE) with a desiccant canister and pharmaceutical polyester coil. The closure consists of a polypropylene child resistant cap with a polystyrene foam inner seal.

Active substance

Sevelamer is a non-absorbed phosphate binding poly (allylamine hydrochloride) polymer consisting of 60 % free amine and 40 % amine hydrochloride. It is a white to off-white hygroscopic powder, insoluble inaqueous and organic solvents.

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Sevelamer does not have a distinct melting point. Differential Scanning Calorimetry demonstrates that sevelamer is an amorphous polymer with a single glass transition at about 118°C. X-ray powder diffraction analysis has also shown that sevelamer is amorphous with no crystalline structure.

The synthesis of sevelamer consists of crosslinking poly (allylamine hydrochloride) with epichlorohydrin.The product is washed, dried and ground to the desired particle size to give the active substance sevelamer.

Several analytical techniques have been used to characterise sevelamer. The quality of the active substance is assured by the specifications and the proposed methods are adequately validated.

Impurities described for the active substance are residual starting materials, inorganic impurities and residual solvents. There are no significant degradation products. Impurities have been shown to be adequately removed in the washing steps or their levels are controlled through preset specifications.

A re-test period of 12-months for the active substance, when stored at 25°C, was considered acceptable.

Other ingredients

The excipients used in the formulation, colloidal anhydrous silica and stearic acid, are added to improve the flow of the blend. The excipients comply with Pharmacopoeial monographs.

The capsule shells arehard gelatin capsules (elongated, size 0) containing gelatin and titanium dioxide. Sodium lauryl sulphate and silicon dioxide are added as manufacturing aids to the gelatin.

Two of the excipients, stearic acid and gelatin, may be of bovine origin. Satisfactory assurance of compliance with the CPMP Note for guidance on minimising the risk for transmitting animal spongiform encephalopathy agents via medicinal products (CPMP/BWP/1230/98) has been provided.

Product development and finished product

The aim of the pharmaceutical development was to prepare an immediate release oral dosage form that would disintegrate in the stomach. It has been demonstrated that the excipients do not affect the *in vitro* phosphate binding. The final formulation enables high speed encapsulation while producing capsules containing a large amount of active substance.

The manufacturing process is a conventional process for oral solid capsules consisting of 3 principal steps: sieving, blending and capsule filling. Validation of the process has been carried out and in-process controls are acceptable.

Control tests on the finished product include identification of the active substance, determination of phosphate binding capacity, uniformity of mass, loss on drying, disintegration time and visual description. Results from analyses of 12 commercial scale batches confirm the satisfactory uniformity of the product at release.

For the finished product 24 months stability data at 25°C/60%RH and 12 months at 40°C/75% RH are available, and support the storage conditions and shelf-life as defined in the SPC.

Renagel Film coated tablets:

Renagel is presented in this formulation as film-coated tablets containing 400 mg or 800 mg of sevelamer.

Tablets are off-white; oval shaped and imprinted with “RENAGEL 400” or “RENAGEL 800”on crown in black ink, single side.

The primary packaging material is composed of high-density polyethylene bottles (HDPE) bottles. The closure consists of a polypropylene child resistant cap.

Active substance

Sevelamer is the same active substance as that used in the previously approved Renagel 403 mg hard capsules. Genzyme Ltd, Haverhill, UK, can supply it by the Dow Chemical Company or.

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Other ingredients

The tablet cores contain the same excipients as the approved capsules formulation, although in different quantities: Silica colloidal anhydrous and stearic acid complient with the specifications and test methods of the Ph. Eur.
The film coating contains hypromellose, purified water and diacetylated monoglycerides.
Substances of animal origin covered by the scope of the TSE guideline (EMEA/CPMP/BWP/1230/98/rev.1) are not included in, or used during the manufacture of Renagel film-coated tablets.
Stearic acid and diacetylated monoglycerides are of vegetable origin.

Product development and finished product

Sevelamer in an insoluble non-absorbed crosslinked polymer that binds phosphate in the small intestine. The manner of dosage is such that Renagel is titrated until the desired serum phospate level is achieved.
The objective of the Renagel film-coated tablet development program was to reduce dosage size and/or decrease the number of units required for dosage administration. To accomplish these objectives, it was necessary to maintain a high concentration of active substance in the formulation. The tablet dosage form also needed to retain the efficacy and immediate release characteristics of the capsule dosage form.
The objective of the tablet coating was to provide a swallowable tablet, which would retain the immediate release characteristics of the capsule formulation. Coating strength and elasticity were evaluated by exposing tablets (open container) to accelerated stability conditions, 40°C/75% RH. Under these conditions the tablets absorb moisture (about 30% by weight), which tests the strength and elasticity of the coating and allows "weak" coatings to be identified because the coatings split. A conventional hypromellose coating was identified which had the desired characteristics when coating levels were greater than 4%. Tablets with this coating were prepared on scales from 5 to 170 kg, and these runs confirmed that the desired characteristics (coating strength, disintegration times) were achieved.

No overages are included in the formulations.

Stability of the Product

The stability data show that the tablets meet the proposed shelf life specifications during storage for 12 months at the long-term conditions (25°C±2°C / 60%± 5% RH) and also at the accelerated conditions (40°C±2°C / 75%±5% RH). The loss on drying results slightly increased at all conditions and were more pronounced at 40°C±2°C / 75%±5% RH. The results showed no increase in the microbial burden of Renagel tablets; total aerobic count was always < 100 CFU/g, total moulds and yeasts < 100 CFU/g and St. aureus, Ps. aeruginosa, Salmonella and E. coli were absent.

The proposed shelf life is 24 months when stored at the recommended storage conditions (not above 25°C, the container tightly closed).

Bioequivalence

Because Renagel is not absorbed, a conventional human pharmacokinetic study to demonstrate that Renagel film-coated tablet is bioequivalent to the capsule formulation is not appropriate. Therefore in vitro phosphate binding studies for the purpose of showing equivalence have been used. The objective of the studies was to determine if the disintegration times and phosphate uptake profiles of the two dosage forms are comparable. All results demonstrate that the film-coated tablet and capsule disintegration and subsequent phosphate binding are equivalent.

3. Toxico-pharmacological aspects

Pharmacodynamics

The pharmacodynamic action of sevelamer has been studied *in vitro* and *in vivo*.

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Sevelamer contains partially protonated polymer amines, which become close to fully protonated after the capsule disintegrates in the stomach. As phosphate is liberated during digestion, the free phosphate can diffuse into the polymer and interact with the protonated (cationic) polymer amines. Phosphate is preferentially bound because it is polyvalent. The four oxygen atoms in the phosphate molecule are capable of ionic or hydrogen bonding interactions with the protonated or unprotonated amines of sevelamer.

Several short term (4-5 day) animal studies were conducted to investigate the phosphate binding capacity of sevelamer *in vivo*. Oral administration of sevelamer to rats significantly increased faecal excretion of phosphate and decreased urinary phosphorus levels.

Studies on urinary and serum electrolytes in rats provide evidence that sevelamer releases chloride ions (Cl^-) in exchange for hydrogen phosphate (HPO_4). This was confirmed in the repeat dose toxicity studies in rats and dogs. In addition to binding dietary phosphates, sevelamer significantly increased faecal excretion of bile acids which indicates that it also binds bile acids due to its ion exchange properties. This may lead to changes in absorption of fat-soluble vitamins and cholesterol. It may also affect the pharmacokinetics of drugs having enterohepatic circulation.

The applicant did not test the receptor binding profile of sevelamer, which was accepted due to the physiochemical properties of the compound and the absence of any measurable pharmacodynamic effects excluding its phosphate binding properties.

The secondary pharmacology of sevelamer has been adequately investigated. The only effect of sevelamer found in secondary pharmacology studies was an increased resting tension of guinea pig ileum and rat gastric fundus. Sevelamer was devoid of any measurable effects on general behaviour, locomotor activity or other CNS activity, body temperature, cardiovascular or respiratory control in experimental animals. These findings are in line with the known mode of action of sevelamer and the lack of absorption from the intestine. An additional safety pharmacology study was conducted to investigate the effects of chronic sevelamer treatment (10% w/w in diet for 2 weeks) on blood coagulation in rats. At necropsy, haemorrhages in the testes and epididymides were observed in one male. In both males and females, activated partial thromboplastin time (APTT) was significantly prolonged when compared to the untreated animals. Platelet counts were also lower in sevelamer treated animals. No changes were observed in the fibrinolytic system as measured by euglobin clot lysis time. This may be due to reduced absorption of dietary vitamin K.

Pharmacokinetics

Single dose and repeated dose pharmacokinetics have been investigated in the rat and dog using radiolabelled sevelamer. Neither whole body autoradiography nor liquid scintillation counting of blood, urine, bile and tissue samples could detect significant amount of radioactivity. It was therefore, concluded that sevelamer is not absorbed from the gastrointestinal tract. In *in vitro* studies, no significant degradation of sevelamer was demonstrated in simulated gastric fluid (pH 1.2 + pepsin) and in the gastrointestinal contents of rats.

In rats, excretion of radioactivity in the faeces following intake of radiolabelled sevelamer was 20-80 % after 12 hours and more than 90 % after 24 hours. Faecal excretion was a little slower in dogs: 30 % after 12 hours, 50-75 % after 24 hours and 90% after 48 hours. Sevelamer is excreted almost entirely in the faeces. Only trace amounts of radioactivity were found in the urine.

The applicant conducted some preclinical drug interaction studies. Studies in beagle dogs showed that absorption of estrone, propranolol and thyroxine may be delayed by concomitant absorption with sevelamer. *In vitro*, sevelamer was shown to bind a number of anionic drugs. However, the relevance of *in vitro* data is very limited since a number of compounds, including phosphates will compete with drug binding to sevelamer.

Toxicology

Single dose toxicity in rodents and dogs showed that sevelamer-administered p.o. has a low acute toxicity profile, with the highest doses tested being well tolerated.

Repeated dose toxicity of sevelamer after oral administration was studied in rats (up to 26 weeks) and dogs (up to 52 weeks). Chronic sevelamer treatment was generally well tolerated. In the rat studies increased numbers of hemorrhages were found, particularly in males at high dose groups (10

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g/kg/day). The applicant considered that this effect was likely to be due to reduced absorption of fat-soluble vitamins and particularly that of vitamin K. Evidence for that was seen in prolongation of protrombin time and/or APTT. When high dose sevelamer was given with fat-soluble vitamins D, E and K, no hemorrhages were seen in groups of mice or rats. No target organ toxicity was observed in rats or dogs as evidenced by gross anatomical observations and histopathological studies. Some evidence of gastrointestinal toxicity was found in rats, as gastric mucosa thickening was occasionally seen (a dose-dependent phenomen in female rats). In addition, eosinophilic crystalloid material, which is likely to be sevelamer based, was found in intestinal lumen in high dose rats. A possible explanation for this is that high dose sevelamer could induce submucosal oedema due to increased osmotic pressure. These findings were not considered to be of clinical relevance.

Other observations in rats and dogs were decreased levels of vitamin D and E, and serum cholesterol. The preclinical observations on fat-soluble vitamins have been noted in section 5.3 of the SPC. Furthermore, in rats sevelamer seemed to increase serum levels of copper at high doses (15-30 x human doses). In a number of studies serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and blood urea nitrogen increased in both male and female animals. Possible mechanisms for these enzyme level rises remain unexplained. However, since rises were moderate and there were no histopathological findings in organs, these observations are probably of no clinical relevance.

Reproduction toxicity was adequately investigated in rats and rabbits, although peri-and postnatal studies were not performed. Given the intended use of sevelamer and lack of its systemic absorption, this can be accepted. In high doses (1 to 4.0 g/kg/day) reduction in foetal ossification was found in rats. This was probably related to reductions in vitamin D and/or reduction in absorption of phosphates from the gastrointestinal tract.

Sevelamer was non-mutagenic in the Ames test. In Chinese Hamster Ovary cells, sevelamer induced a slight increase of structural chromosomal aberrations at high concentrations only. This was suggested to be due to sevelamer's ability to absorb the culture medium and not direct action. In the mouse micronucleus test *in vivo* sevelamer was negative.

Currently, no formal carcinogenicity data are available. However, in vitro and in vivo studies have indicated that Renagel does not have genotoxic potential. Also the medicinal product is not absorbed in the gastrointestinal tract.

4. Clinical aspects

The clinical program aimed to demonstrate that Renagel is an effective phosphate binder for the reduction of serum phosphate levels in patients with end-stage renal failure (ESRF) onhaemodialysis. The clinical documentation consisted of a total of 12 studies, 6 phases I studies in 136 healthy volunteers, 3 phase II studies and 3 phase III studies in a total of 408 ESRF patients, with one extension study in 192 patients.

Clinical pharmacology

A summary of phase I studies conducted with Renagel is provided in Table 1.

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Table 1: Overview of Phase I studies with Renagel

Protocol/ Reference	Study Design	Dose of Renagel (g/day)*	Other Therapy	Duration	No. Healthy Volunteers
GTC-02-101/1	Double blind, placebo controlled, parallel group	2.85 to 14.25	Placebo	Single dose 7 day washout 8 days multiple dose (tid)	24
GTC-10-801/2	Open label, parallel group, pk study	6.6 to 7.1	None	Mutiple dose for up to 32 days	20
45/804	Open label, crossover, pk interaction study	2.418	Enalapril, single dose	Single dose, 7-day washout	28
45/803	As above	"	Metoprolol tartrate, single dose	"	31
013821	As above	2.418 for 2 days	Warfarin, single dose	2 days, 14 day washout	14
013769	As above	"	Digoxin, single dose	"	19

* Actual doses expressed as anhydrous dose

Pharmacodynamics

One pharmacodynamic study (study 101) was conducted in 24 healthy volunteers on a phosphate-controlled diet. The objectives of the study were to determine the safety and tolerance of single doses of sevelamer (1, 2.5 and 5 g) and to determine the safety, tolerance and efficacy of multiple doses of sevelamer (placebo or 1, 2.5 and 5 g t.i.d. for 8 days). This study demonstrated the phosphate-binding capacity of sevelamer following repeated administration. A dose-dependent decrease in total urine phosphorus and increases in the ratio of stool to urine phosphorus were observed. Consistent changes in serum phosphorus or calcium concentrations were not observed. Serum cholesterol decreased clinically significantly from baseline in all sevelamer groups (up to 24 % decrease at the highest dose compared to 3 % increases in the placebo group). No serious adverse events occurred during the study. Slight decreases in prothrombin time and vitamin D25 were observed during sevelamer treatment.

Pharmacokinetics

One pharmacokinetic study in 20 healthy young and elderly subjects was conducted. Subjects were given non-radiolabelled sevelamer for 28 days, followed by 5 x 465 mg capsules of ^{14}C-labelled sevelamer as a single dose, then 2.325 g t.i.d. of non-radiolabelled sevelamer for 4 days. Detectable amounts of sevelamer were not present in whole blood. In approximately one third of subjects, 0.02 % or less of the dose was recovered in urine and in all of the subjects except one, at least 90 % of the dose was recovered in faeces within 7 days (mean 99.57 %). The small amount of radioactivity in urine is considered to represent absorbed unbound radiolabel. According to this study, no absorption occurred in healthy subjects at the clinically relevant daily dose of approximately 7g. However, it cannot be ruled out that absorption may increase in presence of bowel obstruction or inflammatory bowel disease.

The pharmacokinetics of sevelamer have not been studied in patients with end-stage renal disease or in any special patient groups.

According to preclinical studies, sevelamer is a bile-acid binding compound. In contrast, four clinical pharmacokinetic interaction studies in healthy volunteers did not reveal any clinically significant interactions between sevelamer and digoxin (known to interact with cholestyramine, enterohepatic circulation), warfarin (known to interact with cholestyramine, positive *in vitro* binding to sevelamer), enalapril (positive *in vitro* binding) and metoprolol. All these drugs are frequently used and medically relevant in the ESRF population. Interaction studies have not been conducted in ESRF patients, where

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drug elimination in faeces becomes even more important than in healthy volunteers. Therefore it is advised to check for interactions on a regular basis.

Efficacy

The applicant presented six clinical studies, one of which was an open extension trial. An overview of these studies is provided in tables 2 and 3.

Description of studies:

Patient population: The efficacy studies enrolled patients with ESRF. The mean age of the patients was approximately 55 years. Approximately half of the patients were African-Americans. The aetiology of ESRF was hypertension in approximately 30 % and diabetes in 23 % to 37 % of patients. Only 0-16 % had received prior aluminium-based phosphate binders, the rest of the patient population had received calcium carbonate or calcium acetate. Approximately 50-67 % received vitamin D. The proportion of patients who had undergone parathyroidectomy ranged from 1% to 13%. The median duration of dialysis ranged from 3.0 to 4.3 years and the mean Kt/V as a measure of effectiveness of dialysis therapy ranged from 1.4 to 1.5, indicating adequate control.

The safety and efficacy of Renagel has not been studied in children, predialysis patients and in patients receiving peritoneal dialysis. The major inclusion criteria in the clinical studies were age = 18 years, haemodialysis for three months or longer, oral phosphate binder treatment (calcium or aluminium), stable vitamin D dose (or no vitamin D), stable diet, negative pregnancy test and an acceptable contraceptive method. Patients with poorly controlled diabetes mellitus or hypertension, intestinal motility disorder, abnormal or irregular bowel function or history of major gastrointestinal tract surgery were excluded from the efficacy and safety studies. Other major exclusion criteria included history of swallowing disorders, use of antiarrhythmic or seizure medications, evidence of malignancy except for basal cell carcinoma of the skin, and substance abuse. This information has been included in the SPC.

Efficacy parameters: The primary efficacy measure in all of the studies was the change in serum phosphorus (Pi) from washout to end of treatment. Secondary variables included serum calcium, calcium x phosphorus, serum intact parathyroid hormone (iPTH), cholesterol, LDL cholesterol and triglycerides.

There is, currently, no well-defined threshold for the benefit of lowering S-Pi. The study protocols defined S-Pi response as a decrease to 1.78 mmol/l [5.5 mg/dl] or less, or return to prewashout levels (i.e. concentration preceding washout). At the request of the CPMP the effect of sevelamer in all the dose titration trials was analysed with a responder defined as a decrease to less than 1.78 mmol/l [5.5 mg/dl].

Exploratory studies/Phase II: three phases II studies enrolling a total of 180 patients (147 received sevelamer) have been carried out, as summarised in Table 2 below.

Table 2: Overview of Phase II studies with Renagel

Protocol/ Reference	Study Design	Dose of Renagel (g/day)*	Other Therapy	Duration	No. Patients Treated
GTC-10-201/3	Double blind, placebo controlled, parallel group	0.95 to 8.0	Placebo	2 weeks $CaCO_3$ or CaAC 2 weeks washout 2 weeks Renagel or placebo	36
GTC-10-202/4	Open label, dose titration	0.76 to 7.4	None	2 weeks washout 8 weeks Renagel 2 weeks washout	48
GTC-36-203/5	Open label, dose titration, parallel group	0 to 11.0	$CaCO_3$ supplements (2.25 g/day)	2 weeks washout 12 weeks Renagel or Renagel + $CaCO_3$ 2 weeks washout	75

* Actual doses expressed as anhydrous dose

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In *study 201*, dose titration was not possible as the treatment phase of the study was limited to 2 weeks. A total of 38 patients were enrolled and 36 patients received sevelamer (n=24) or placebo (n=12).
In *study 202* patients who were hyperphosphatemic following washout were enrolled. Patients were treated with sevelamer for 8 weeks; the starting dose was determined on the basis of washout S-Pi (500-1500 mg t.i.d. with meals). A total of 48 patients received sevelamer in the study, 28 patients were included in the per protocol analysis (6 did not complete the study, 1 discontinued, 15 non compliers). The final prescribed dose was 12-18 capsules/day (6-9 g/day) in the majority of patients.
Study 203 was a 12-week dose titration study of Renagel vs. Renagel with evening dose of calcium carbonate. Calcium supplements were given to overcome possible hypocalcaemia. Patients who were hyperphosphatemic following washout were enrolled. A total of 94 patients were screened, 75 received study medication and 55 patients completed the study. The starting dose was adjusted according to washout S-Pi. The mean dose was 3.9 g/d for week 1-3 of treatment, 4.4 g/d for week 4-6, 5.0 g/d for week 7-9, and 5.1 g/d for week 10-12 of treatment.

Main studies:
The phase III studies were of open-label design. The studies consisted of one crossover study comparing sevelamer and calcium acetate (8 weeks) and one dose titration study (8 weeks, sevelamer alone) enrolled a total of 326 patients (256 received sevelamer). There was one uncontrolled, extended use study (up to 44 weeks) in 192 patients.

Table 3: Overview of Phase III studies with Renagel

Protocol/ Reference	Study Design	Dose of Renagel (g/day)*	Other Therapy	Duration	No. Patients Treated
GTC-36-301/6	Open label, dose titration, crossover	0 to 12.6	CaAc (2 to 12 g/day)	2 weeks washout 8 weeks Renagel or CaAc 2 weeks washout 8 weeks Renagel or CaAc 2 weeks washout	84
GTC-36-302/7	Open label, dose titration	0.88 to 11.0	None	2 weeks washout 8 weeks Renagel 2 weeks washout	172
GTC-36-901/8	Open label, dose extension	1.8 to 10.3	None	2 weeks washout 44 weeks Renagel 2 weeks wshout	192 +

* Actual doses expressed as anhydrous dose
\+ Patients who previously received Renagel in a clinical study (includes 7 treatment naive patients).

Study 301 was an open-label crossover study of Renagel and calcium acetate. Treatment duration was 8 weeks and the starting dose was based on the degree of hyperphosphataemia and ranged from 0.93 to 1.86 g t.i.d. The starting doses of calcium acetate ranged from 0.677 to 2.0 g t.i.d. Dose were subsequently adjusted to achieve a S-Pi of 2.5-5.5 mg/dl. The Intent-to-treat (ITT) population consisted of 83 patients and the per-protocol (PP) population of 35 patients. Fourteen patients were excluded due to less than 8 weeks of treatment, 27 due to less than 70 % compliance, and 7 patients due to failure to maintain a stable vitamin D dose. The overall mean actual daily dose for Renagel and calcium acetate in the ITT population was 4.3 and 4.4 g/day. Compliance was comparable in the groups (79% and 78%) in the ITT population.

Study 302 was an open-label, uncontrolled dose titration study of 8 weeks duration. Following the screening period, patients entered a 2-week phosphate binder washout period. Renagel treatment was given to patients who became hyperphosphatemic (serum phosphate > 6.0 mg/dL). Starting doses of sevelamer were 0.93-1.86 g t.i.d depending on washout S-Pi. Dose was subsequently adjusted as in study 301. The ITT population consisted of 168 patients and the PP population of 107 patients. 28

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patients were excluded due to less than 8 weeks of treatment, 25 due to less than 70 % compliance, 8 patients due to failure to maintain a stable vitamin D dose, and 2 patients prescribed calcium carbonate. The mean actual daily dose for Renagel in the ITT and PP populations was 10.7 and 11.4 capsules per day respectively. Compliance was 85 % in the ITT population.

Study 901 is an extended-use (up to 44 weeks) study in 192 patients, which focused on long-term safety. The majority of patients had received Renagel for 8-12 weeks in their preceding study (202, 203, 301 or 302). The extension protocol allowed the use of variable vitamin D and dietary calcium supplements, which were adjusted at the discretion of the investigators. Of the 192 patients, 34% used Renagel plus calcium supplements with average doses of 800 mg of elemental calcium. At study entry, 74% of patients were using vitamin D (66% i.v. and 8% oral). During the study 34% had a net increase in vitamin D with 11% initiating vitamin D. Eleven percent of patients had a net decrease in vitamin D dose.

Results

Serum phosphate: The mean changes observed in the primary efficacy variable S-Pi are summarised in table 4 below:

Table 4: Changes in serum phosphate (mmol/L)

Study Number	202*	203*		301*		302*	901**
		Renagel	Renagel +Calcium	Renagel	Calcium Acetate		
N	48	35	36	80		166	192
Mean	-0.45	-0.77	-0.74	-0.65	-0.68	-0.81	-0.71
Median	-0.42	-0.87	-0.68	-0.68	-0.71	-0.81	-0.71
Std dev	0.65	0.58	0.71	0.74	0.61	0.74	0.77
Lower 95% CI	-0.63	-0.96	-0.97	-0.81	-0.81	-0.92	-0.82
Upper 95% CI	-0.27	-0.58	-0.51	-0.49	-0.55	-0.70	-0.60
p-value	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* ITT population
** Safety population

Renagel resulted in a statistically significant decrease in serum Pi from baseline (washout). Using the definition of S-Pi response as defined in the protocols (decrease to 1.78 mmol/l [5.5 mg/dl] or less, or return to prewashout levels), there were no statistically significant differences between treatments in studies 203 and 301.

At the request of the CPMP the effect of sevelamer was analysed with a responder defined as a decrease to less than or equal to 1.78 mmol/l [5.5 mg/dl]. Dose response was modelled in the largest of the phase III studies (study 302). To provide information on the average dose, patients were categorised by the severity of their baseline hyperphosphataemia into one of three levels as specified in the protocol. The results are provided in table 5.

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Table 5: The mean doses of Renagel required to lower S-Pi to less than or equal to 1.78 mmol/l in study 302

Mean Dose of Renagel (grams)	Baseline serum phosphate (mmol/l)
3.4	1.78 to <2.42
5.3	2.42 to < 2.91
6.3	= 2.91

The results support the starting doses of 2.4 grams, 3.6 grams and 4.8 grams based on serum phosphate level as recommended in the SPC.

Serum calcium: Generally, a modest effect (increase) on serum calcium was observed when Renagel was used alone. When combined with 3 x 750 mg calcium carbonate, slight increases were observed. However, in study 301, statistically significant increases in S-Ca were observed in both Renagel and calcium acetate groups, although the increases were clearly more marked in the latter group. When used alone (without calcium supplements), the risk of hypercalcemia may be smaller during Renagel treatment compared with calcium acetate. This is reflected in the results of study 301(incidence of hypercalcemic events was 18.5% in the Renagel group and 45.1% in the calcium acetate group, p=0.002). There is no data on the relative risk of hypercalcemias compared with alternatives (Ca-based phosphate binders) when Renagel is used in combination with both calcium supplements and adjustable vitamin D (actually in the majority of patients in the clinical setting). This issue will be addressed further in a long term comparative study which will be undertaken by the applicant.

Serum intact parathyroid hormone (iPTH): Renagel alone did not consistently suppress iPTH to a clinically significant degree and was clearly less effective in iPTH control than calcium acetate. Renagel should, therefore, be used in a multitherapeutic approach including vitamin D and/or calcium "supplements" (see SPC).

Calcium x Phosphorus product (Ca x Pi): A consistent and significant reduction in Ca x Pi product was observed with Renagel alone or combined with calcium supplements. The reduction after 8 weeks was of similar magnitude to that observed during calcium acetate treatment. At this stage conclusions cannot be drawn on the effect of Renagel on Ca x Pi product when used together with calcium supplements and/or adjustable vitamin D compared to established treatment, but the use of Renagel with calcium supplementation does not pose a safety risk with regard to calcium x phosphorous product. The CPMP, therefore, agreed that this could be addressed further in the randomised comparative study, which will be undertaken by the applicant.

Cholesterol, LDL cholesterol and triglycerides: Total cholesterol and LDL cholesterol decreased during Renagel treatment, while HDL cholesterol and triglycerides did not change. This has been reflected in the SPC. Low HDL and elevated triglycerides are not an uncommon combination in ESRF patients.

Interestingly, the changes in serum phosphorus and LDL cholesterol were significantly greater in non-African-American as compared to African-American. As Renagel dose will be individualised according to serum Pi concentration, this difference is not considered to warrant special precautions.

Clinical studies in special populations

The safety and efficacy of Renagel has not been studied in children. This information is included in the SPC.

Clinical safety

The assessment of safety of sevelamer is based on data from 384 patients who received sevelamer and includes phase II and III studies, with the exception of study 201 (excluded due to the short treatment period and low doses of sevelamer used).

With regard to sevelamer dose, 28% of the patients were in the low group (<4.5 g), 28% were in the medium dose group (4.5-6.0 g) and 43% were in the high dose group (>6.0 g). The mean duration of exposure was 172 days (25 weeks). There was a significant difference across the dose groups for age category: the percentage of patients less than 55 years of age was 28% in the low dose group and 66% in the high dose group. Mean length of exposure was higher in the high dose group compared to low dose group.

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Of the 384 patients exposed to Renagel in the pooled analysis, 58 discontinued due to adverse events, 20 withdrew consent, 13 terminated due to death, 2 were terminated due to non-compliance, 4 were lost to follow-up and 22 were discontinued due to "other reason". Six additional patients died following study discontinuation or completion.

Overall, a total of 81 adverse events required discontinuation. Of these, 17 adverse events were judged possibly or probably related. These consisted of vomiting, nausea, heartburn, gagging, insomnia and poor appetite, abdominal pain, acne and dry skin, worsened hair loss, diarrhoea and dyspepsia.

The relatively large overall rate of adverse events (91%) is probably a reflection of the patient population. Body as a whole was the body system with most frequent occurrence (68%). Within this body system, pain was the most frequent adverse event (30%). The next most frequent body system was the digestive system (63%). Gastrointestinal undesirable effects are expected.

Overall, 27% of patients had mild AEs, 37% experienced moderate and 28% experienced severe adverse events. There was no overall difference between males and females in the frequency of adverse events.

Treatment-emergent adverse events judged as possibly or probably related to study treatment were experienced by 35% of patients and the frequencies were comparable across the dose groups. 18% experienced mild, 16% moderate and 1% severe adverse events. There was no clear relationship between dose and severity or dose and frequency. Five treatment-emergent adverse events showed a significant trend with regard to sevelamer dose: accidental injury (10%, 11% and 19%), cardiovascular disorder (1%, 2% and 7%), coughs increase (7%, 12% and 19%), pharyngitis (1%, 5% and 10%) and rash (0%, 2% and 5%). The clinical significance of these findings remains unclear, and they have been listed in the SPC accordingly.

Case narratives of all deaths were provided in the dossier. Fourteen of the 19 deaths were due to cardiovascular causes, three due to infection, one due to renal carcinoma and one due to homicide. It is recognized that 40% of deaths in ESRF patients are due to cardiovascular causes. None of the deaths were judged related to Renagel treatment.

Altogether 290 serious adverse events were reported in 140 patients (37%). A dose trend was only observed for congestive heart failure (inverse trend) and gastrointestinal hemorrhage (inverse trend). The largest proportion of SAEs was reported for the cardiovascular system.

No consistent or clinically meaningful changes in serum electrolytes attributable to treatment were evident. Dose-related increases were observed in serum alkaline phosphatase and bone-specific alkaline phosphatase. In the highest dose group serum alkaline phosphatase increased from a normal mean value to a mean value at the upper limit of normal. The increase in bone-AFOS was approximately 54-56%. Liver alkaline phosphatase tended to decrease. The increases observed in bone-AFOS raise concern with regard to the risk of osteitis fibrosa, although the applicant considered these changes clinically unimportant. No clinically significant changes were observed in ALT, serum protein, prealbumin or globulin.

With regard to complete blood cell count data, slight, but statistically significant changes were observed in platelet count, red cell count (decrease), Hb (decrease), MCHC (decrease), MCV (increase). Any possible effect on iron absorption would be hidden due to changes in iron preparation dose on demand based on follow-up of iron status. In the absence of comparative long term data, clinically significant effects on iron absorption cannot be excluded. However, iron status is routinely monitored in dialysis patients.

With regard to folate, a trendwise decrease during only 8 weeks of treatment is suggested by the data based on one small (n=83) uncontrolled study. Possible development of folate deficiency during long term treatment cannot be excluded. Folate status is not part of routine follow up. A recommendation to monitor folate status during treatment has been included in Section 4.4. of the SPC.

Fat soluble vitamins are of special interest due to the bile acid binding characteristics of sevelamer.

As expected due to the LDL cholesterol lowering effect of sevelamer, vitamin E levels decreased slightly. Sevelamer did not appear to have clinically significant effects on the absorption of vitamin A in short-term studies, and based on coagulation parameters, vitamin K status was not adversely affected. However, clinically significant effects cannot be ruled out in the intended long-term use of

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sevelamer. Furthermore, the patients included in these studies were probably not undernourished and did not have significant gastrointestinal pathology. Until more experience of long-term use is gained, a warning that patients may develop low vitamin A, D, E and K levels has been included in section4.4 of the SPC, with a recommendation that levels of these vitamins be monitored and supplemented if necessary.

Serum chloride may increase during Renagel treatment as chloride may be exchanged for phosphate in the intestinal lumen. Although, no clinically significant increase in serum chloride was observed during clinical studies, a recommendation that serum chloride be monitored as done in the normal follow up of a dialysis patient is included in the SPC.

5. Overall Conclusions and benefit risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Products Characteristics (SPC). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. A number of minor chemical and pharmaceutical issues remained at the time of the CPMP Opinion and will be resolved as follow-up measures.

Pre-clinical pharmacology and toxicology

The main pharmacodynamic effect of sevelamer and its mechanism of action have been adequately demonstrated in the primary pharmacodynamic studies. The secondary pharmacology studies showed that sevelamer is devoid of any measurable effects on general behaviour, locomotor activity or other CNS activity, body temperature, cardiovascular or respiratory control in experimental animals. Preclinical pharmacokinetic studies demonstrated that sevelamer is excreted entirely in the faeces without significant systemic absorption.

Overall, the toxicology program revealed that sevelamer is generally well tolerated without any major signs of systemic toxicity. The decreased serum levels of vitamin D, vitamin E and folic acid as well as the coagulation defect detected at high doses in rats, likely to result from vitamin K deficiency, can be ascribed to adsorption of the vitamin itself (folic acid) or of biliary acids to the polymer. This information has been included in the SPC.

Efficacy

A consistent and clinically significant effect of sevelamer on serum phosphorus in haemodialysis patients has been demonstrated in short term (up to 2 weeks double-blind vs. placebo, up to 8 weeks open vs. calcium acetate) crossover trials. No comparative long-term data are available on the effects of Renagel on serum phosphorus in haemodialysis patients. The CPMP accepted, however, that in the ESRF population receiving haemodialysis treatment, it would be ethically problematic to perform long term double blind placebo-controlled studies due to risks involved with hyperphosphatemia. It was also recognised that suitably masked controlled parallel group studies vs. calcium-based binders can be problematic because calcium based binders may be easily identified by experienced patients because of their texture and because they lead to predictable increases in serum calcium, whereas Renagel does not. This was highlighted in the open-label randomised cross-over study 301.

The clinical programme was limited in that the studies were performed in a relatively small number of patients who were on chronic haemodialysis treatment. Predialysis patients, paediatric patients and patients receiving peritoneal dialysis were excluded. None of the controlled studies were carried out under conditions mimicking the actual setting in which this treatment option would be used. In ESRF patients the control of hyperparathyroidism is closely linked to the treatment of hyperphosphatemia. The standard management of both conditions consists of dietary phosphate restriction, dialysis, phosphate binders and vitamin D. Calcium based phosphate binders decrease S-Pi and increase S-Ca. Both factors suppress iPTH. If iPTH suppression is not sufficient, vitamin D is used.

Renagel decreases S-Pi, but has a modest effect on calcium. Whether Renagel has a clinically significant effect on iPTH has not been consistently demonstrated. In clinical practice the majority of ESRF patients will need vitamin D to control secondary hyperparathyroidism and calcium supplements

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in case of hypocalcaemia, as noted in the SPC. Only the uncontrolled extension study 901 provided information on the combined use of Renagel with calcium supplements and/or adjustable vitamin D in the "real life setting".

To clarify the role of Renagel in the management of secondary hyperparathyroidism in the unavoidable combination treatment setting, a long term comparative study vs. calcium-based phosphate binders with or without adjustable vitamin Dwill be conducted.

Safety

The safety database had its limitations, in that there was a ”relative lack” of controlled trials. However, on the basis of the data provided, the CPMP considered the overall safety profile of sevelamer to be acceptable. Safety has been adequately demonstrated during short-term treatment, with undesirable effects consisting of mainly gastrointestinal symptoms and the extension trial (study 901) suggested a similar safety profile.

Benefit/risk assessment

Although there were limitations in the clinical data, the CPMP acknowledged that a consistent and clinically significant effect of sevelamer on serum phosphorus in haemodialysis patients had been demonstrated. The safety profile of sevelamer is acceptable. Further data from a longer term controlled clinical trial was requested by the CPMP.

During an oral explanation held before the CPMP on 21 September 1999, the applicant addressed the place of Renagel compared to standard therapy and the additional clinical data that would be provided as post-authorisation commitments.

To address the need for comparative long term data on the effects of Renagel on serum phosphorous, calcium and iPTH in haemodialysis patients, as well as effects on bone, the applicant committed to perform additional clinical studies.

Based on the data available on quality, safety and efficacy, the CPMP considered by consensus that the provisional overall benefit/risk profile of Renagel is favourable. The CPMP adopted a favourable opinion under exceptional circumstances for granting a marketing authorisation for Renagel for the control of hyperphosphatemia in adult patients on haemodialysis, within the context of a multiple therapeutic approach.

The applicant agreed to provide the additional clinical data requested within a specific timeframe. These data will form the basis of a re-assessment of the benefit/risk ratio of Renagel.

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