LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fosrenol
(lanthanum)

SE/H/481/01-04/E01

This module reflects the scientific discussion for the approval of Fosrenol during a second-wave mutual recognition procedure (MRP). The original MRP was finalised on March 1, 2005. The second-wave procedure was finalised at July 12, 2006. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Fosrenol chewable 250mg – 1,000 mg tablets, contain lanthanum (as lanthanum III carbonate hydrate) as the active moiety. The product is indicated "*as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)*".

Lanthanum carbonate belongs to a new class of non-calcium dietary phosphate-binders. In the acid environment of the stomach the La^{3+} ion is released. The ion binds to dietary phosphate to form insoluble lanthanum phosphate to reduce absorption of dietary phosphate.

II. QUALITY ASPECTS

II.1 Introduction

Fosrenol is presented in the form of chewable tablets containing lanthanum carbonate hydrate corresponding to 250 mg, 500 mg, 750 mg or 1000 mg of lanthanum. The excipients of the formulation are dextrates (hydrated), colloidal anhydrous silica, and magnesium stearate. The tablets are packed in white cylindrical HDPE bottles containing a rayon coil fitted with a tamper evident, child resistant polypropylene screw cap.

II.2 Drug Substance

The drug substance lanthanum carbonate hydrate does not have a monograph in the Ph Eur, and information on the drug substance has been supplied in the main dossier (no ASMF).

Lanthanum carbonate hydrate is a *white to almost white powder* which is *poorly* soluble in water and insoluble in organic solvents. The structure of Lanthanum carbonate hydrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on solubility, hydrate state, and polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Fosrenol chewable tablets are formulated using excipients described in the current PhEur, except regarding dextrates which are controlled according to USP/NF. The raw materials used in the product are either of mineral or vegetable origin or its compliance with the PhEur monograph Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products has been demonstrated by a TSE Certificate of suitability.

The product development has taken into consideration the physico-chemical characteristics of the active substance, *such as* phosphate binding efficiency, solubility, and hydration state. Other aspects addressed were choice of excipients, dosage form solubility, process development, and stability properties.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the drug product specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC, with no special storage precautions needed.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Comprehensive studies of the pharmacodynamics, pharmacokinetics/toxicokinetics and toxicity of lanthanum have been performed in several animal species. When required, studies were GLP-compliant. For oral studies in rodents (mice, rats) and rabbits, lanthanum carbonate was suspended in carboxymethyl cellulose. In oral studies in the dog, lanthanum was administered in gelatine capsules. The toxicity of high systemic levels of lanthanum was studied in the mouse, rat and dog after i.v. administration of lanthanum chloride dissolved in saline.

III.2 Pharmacology

Lanthanum carbonate has been demonstrated *in vitro, ex vivo* and *in vivo* to be an efficacious phosphate binder. As evident from repeated dose toxicity studies, lanthanum carbonate shows long-term efficacy with respect to phosphate binding.

Although lanthanum carbonate appeared to reduce the absorption of calcium from the gut in an *ex vivo* secondary pharmacodynamic study, there were no effects on plasma calcium and only little effect on urinary calcium in repeat-dose toxicity studies in healthy animals. Likewise, in healthy animals, there were no signs of bone disease or tissue calcification at long-term administration. In uraemic rats, there was increased urinary excretion of calcium (no effect on plasma calcium) as well as osteomalacia. However, the most likely cause of osteomalacia in uraemic rats was hypophosphataemia rather than disturbances in calcium metabolism or any direct effect of lanthanum on bone.

Lanthanum carbonate had no effects on vital body functions – CNS, cardiovascular system (including QTc prolongation *in vivo*) or respiration. Gastric effects were evident after oral administration of lanthanum carbonate, such as reduced acidity and delayed emptying.

III.3 Pharmacokinetics

Systemic absorption of lanthanum after oral administration of lanthanum carbonate is very low. The overwhelming part of an oral dose is excreted unchanged via faeces. However, there is extensive evidence for the existence of several deep tissue compartments for the storage and accumulation of the small amounts of La^{3+} ions that are absorbed from the gastro-intestinal tract. Since tissue lanthanum concentrations in repeat-dose toxicity studies were higher than

plasma levels, often by several orders of magnitude, conventional data on plasma pharmacokinetics/toxicokinetics are of little interest and relevance for the safety assessment. In repeated dose toxicity studies, including carcinogenicity studies, high multiples of clinical doses were used. However, systemic (plasma) exposures were close to clinical exposure. The use of higher doses in pre-clinical studies would not have resulted in higher plasma exposures due to the low oral absorption of lanthanum from lanthanum carbonate and the sub-proportional increase in absorption with increasing dose. Very high systemic (plasma) exposures to lanthanum were attained in animal studies with intravenous administration of lanthanum chloride.

Lanthanum does not accumulate in plasma at repeated oral administration of lanthanum carbonate. Tissue accumulation is seen particularly in the gastro-intestinal tract and the lymphoreticular system (mesenteric lymph nodes). Bone and liver also accumulate lanthanum. The distribution pattern of lanthanum is different after i.v. administration of a soluble salt (lanthanum chloride) than after oral administration of lanthanum carbonate. The liver and spleen are the quantitatively most important tissues for accumulation of lanthanum after repeated i.v. injections.

At oral administration, an apparent "steady-state" seems to be attained in some tissues (e.g. the liver), but, in some tissues (e.g. gastro-intestinal tract and bone), levels continued to increase with duration of treatment

Six months after cessation of treatment, measurable, and sometimes very high, levels of lanthanum were still present in tissues. Changes in lanthanum levels with time after withdrawal differed between tissues. In the rat, lanthanum continued to accumulate in some tissues, e.g. bone and mesenteric lymph nodes, after treatment was stopped. This was not seen in the dog, but levels in some dog tissues (bone and liver) decreased very little 6 months after cessation of treatment.

There was an over-proportional increase in some tissue levels with increasing dose. This was particularly obvious for the stomach and other parts of the gastro-intestinal tract in oral studies in both rodents and dogs as well as for the mesenteric lymph nodes in oral rodent studies and the spleen in an i.v. dog study.

For obvious reasons the tissue distribution of lanthanum in human cannot be studied in detail. However, lanthanum has been shown to accumulate in bone in patients (iliac crest samples). With respect to the different aspects of tissue accumulation of lanthanum at repeated dosing, it cannot be decided whether the mouse/rat or the dog is the species most representative of human. Information on the tissue distribution of lanthanum in animal studies has been included in the SmPC (section 5.2).

The chemical form(s) of lanthanum in blood, plasma and tissues has not studied.

III.4 Toxicology

Single and repeated dose toxicity
Orally administered lanthanum carbonate has low acute toxicity.

Repeated dose toxicity following oral administration of lanthanum carbonate was investigated in the rat (2-4-13-26 weeks, doses up to 2000 mg/kg/d) and dog (3 days-2-4-13-26-52 weeks, doses up to 2000 mg/kg/d). Two repeated dose toxicity studies in the mouse (14 days,

13weeks, doses up to 2000 mg/kg/d) were performed as dose range-finding studies for the mouse carcinogenicity study.

Effects on phosphate, calcium and bone
There is evidence of significant accumulation of lanthanum in bone of experimental animals, probably due to the deposition of free La^{3+}-ions, which co-localise with Ca^{2+}-ions. No consistent association with any specific morphological feature in bone was observed. There is also evidence that lanthanum accumulates in bone (iliac crest samples) of patients. At 12 months the median bone level of lanthanum in patients (n=43) was 1 800 ng/g wet tissue (range 120 - 5500 ng/g wet tissue). The median level in patients at 12 months is similar to the median value in dogs given 2000 mg/kg/day for the same period of time. In patients, median and range concentrations at 18 and 24 months were similar to those at 12 months. At 54 months the median bone level of lanthanum in patients (n=11) had increased to 4250 ng/g wet tissue (range 1673 - 9800 ng/g wet tissue). The median value at 54 months is similar to the median concentrations in bone of high-dose (1500 mg/kg/d) mice and rats towards the end of the carcinogenicity studies.

There was no evidence of lanthanum induced bone toxicity in animal studies. Likewise, histological and histomorphometric examinations of bone biopsy samples (iliac crest) from patients treated with lanthanum carbonate revealed no evidence of lanthanum induced bone toxicity.

The MAH has estimated the half-life and time to steady-state in bone from clinical data. In a “realistic scenario” assuming a bone half-life for lanthanum of 2 or 3.5 years (using median or mean estimates, respectively), the MAH has calculated that the deposition in bone after 15 years of exposure would be 9000 or 15 000 ng/g. In a worst case scenario assuming that all absorbed lanthanum accumulates in bone and that no lanthanum is eliminated from bone, 15 years of exposure to 3g/day would result in bone concentrations of 46 000 ng/g (using the highest bioavailability seen in humans) or 14 000 ng/g (using the observed average bioavailability). Generally, non-clinical data from long-term oral repeat-dose toxicity studies support clinical safety at bone levels up to approx. 10 000 ng/g. The SmPC clearly states that safety data exceeding 24 months are limited (section 4.4) and that the risk/benefit from longer-term administration (> 2 years) should be carefully considered (section 4.2).

Most repeated dose toxicity studies included determinations of phosphate in blood and urine, calcium in blood and urine and sometimes plasma parathyroid hormone (PTH) and/or calcitonin. Generally, oral lanthanum carbonate did not induce hypophosphataemia in healthy animals and did not affect plasma calcium. Marked reductions in urinary levels of inorganic phosphate were registered at high dose levels. Both unchanged and increased urinary calcium levels were reported. No consistent changes in PTH or calcitonin were seen. In one study (rat, 26 weeks) femur calcium and phosphate levels were determined. Marginal reductions, although not dose-related, were seen.

All animals were given standard diets with "normal" phosphate levels (rodent diets approx. 0.5%, dog diets approx. 1.5%). Apparently, this was a sufficiently high dietary level of phosphate to compensate for the phosphate loss induced by lanthanum in healthy animals.

In uraemic rats (5/6 nephrectomy), occasional animals given 1000 or 2000 mg/kg/d lanthanum carbonate for 12 weeks developed osteomalacia. The effect of lanthanum carbonate on urinary phosphate excretion was more marked in uraemic rats than in normal rats. In week 12, 57% of nephrectomised rats given 1000 mg/kg/d and 100% of nephrectomised rats given 2000 mg/kg/d had urinary phosphate levels below the limit of quantification (as compared to 0% of

sham-operated rats). It was concluded that the osteomalacia seen in some uraemic rats in the two highest dose groups was secondary to the potent phosphate-binding activity of lanthanum carbonate rather than to a primary toxic effect of lanthanum on bone. Additional supportive arguments for this conclusion include the facts that uraemic rats did not accumulate more lanthanum in bone or show higher plasma levels of lanthanum than healthy rats and that hypophosphataemia (by any mechanism) is known to induce osteomalacia. It was also demonstrated that the bone effects of lanthanum seen in uraemic rats were similar to those induced by feeding a phosphate-deficient diet and that the bone effects seen in uraemic rats treated with lanthanum carbonate could be prevented by supplementing the rats with systemic phosphate (via an osmotic minipump). Another phosphate binder, the non-absorbable sevelamer, given at doses that induced depletion of phosphate, induced the same deleterious effects on bone in uraemic rats as lanthanum. Furthermore, lanthanum had no negative effects on osteoblast function or proliferation.

In conclusion, non-clinical studies do not give any evidence that lanthanum carbonate, at the bone levels determined in the studies, induces any direct/primary bone toxicity in healthy rats, dogs or mice or in uraemic rats.

Hepatotoxicity
I.v. studies with lanthanum chloride in the mouse, rat and dog give clear evidence that lanthanum is hepatotoxic when given by this route. In contrast to the i.v. studies with lanthanum chloride, there is little evidence of any hepatotoxicity in oral studies with lanthanum carbonate. Evidence of hepatotoxicity appeared when liver levels approached 400 000 ng/g tissue (dog, 1 mg/kg/day, i.v., 4 weeks). The nature of the hepatotoxic response with hepatitis and a "diffuse sinusoidal infiltrate consisting predominantly of lymphocytes and macrophages" may signal the presence of levels of lanthanum high enough to precipitate and aggregate into particles activating the lymphoreticular system. No hepatotoxicity was seen in the rat at levels of 53 000-82 000 ng/g (0.3 mg/kg/day, i.v., 4 weeks). The highest liver level attained in any oral study was 7 300-11 050 ng/g (dog, 2000 mg/kg/day, 52 weeks). Liver levels of lanthanum were 3.5 - 5.9-fold higher in uraemic rats than in healthy rats given the same doses of lanthanum carbonate, even though plasma levels were similar. There is no obvious explanation of the higher liver uptake in uraemic rats. At study termination (13 weeks), liver levels were 980 ng/g in healthy rats and 3540 ng/g in uraemic rats given 2000 mg/kg/day lanthanum carbonate. There was no evidence of histopathological liver changes in uraemic rats.

The MAH's calculations of liver levels in patients, based on animal C_{max}:liver concentration or AUC:liver concentration ratios, do not indicate that hepatotoxic liver levels would be reached in the clinic. This calculation assumes that a "steady-state" for liver lanthanum concentration at repeated dosing is attained, a phenomenon for which there is some non-clinical evidence, but no clinical data.

In conclusion, non-clinical studies do not give any evidence that orally administered lanthanum carbonate, at the liver levels determined in the studies, induces any hepatotoxicity in healthy rats, dogs or mice or in uraemic rats. Clinical data do not suggest any lanthanum induced hepatotoxicity.

Effects on the gastro-intestinal tract
In the oral mouse and rat studies there were time- and dose-dependent increases in histopathological stomach changes. In the mouse, epithelial hyperplasia of the glandular and non-glandular regions was seen accompanied by hyperkeratosis of the limiting ridge, and mucosal inflammatory cell infiltration. The NOEL was 100 mg/kg/d. In the rat, gastric changes

included mineralization, epithelial hyperplasia, mucous cell hyperplasia, (sub)mucosal inflammation, eosinophilia of chief cells and hyperkeratosis of the limiting ridge. There was no NOEL for gastric histopathological changes in the 6-month rat study. Similar changes were observed in the rat carcinogenicity study with a NOEL of 100 mg/kg/d.

No histopathological gastric changes were seen in the dog studies.

The histopathological changes in the stomach glandular mucosa in mice and rats, such as glandular hyperplasia, (sub)mucosal inflammation and squamous epithelial hyperplasia of the limiting ridge, are consistent with an irritant/inflammatory response. Stomach glandular mineralization is usually due to deposition of calcium and is a fairly common event in both rodents and dogs, particularly in aged rats, due to disturbances of mineral metabolism, such as in association with renal pathology. However, von Kossa staining of glandular stomach sections for calcium was negative in the 26-week rat study. Electron-dense inclusions in the glandular mucosa of high-dose animals from the carcinogenicity studies (and also in the glandular stomach of dogs in the 52-week study) were observed. It seems possible that the glandular stomach "mineralization", seen in repeated dose toxicity studies in rodents (and carcinogenicity studies) represents the deposition of precipitated lanthanum in view of the demonstrated heavy accumulation of lanthanum in the stomach in repeat-dose oral toxicity studies.

There is no doubt that the non-neoplastic histopathological stomach changes in mice and rats after long-term oral administration of lanthanum carbonate are treatment-related. However, the clinical significance is difficult to evaluate. Gastro-intestinal system disorders were the most common adverse events in clinical trials of lanthanum carbonate, but they were not more common with lanthanum carbonate than with standard therapy. In this context, the results of safety pharmacology studies (decreased gastric acidity and emptying) may also be relevant.

Immunotoxicity
Although mesenteric lymph nodes was a major depository site for lanthanum in repeated dose toxicity studies, there was no evidence from long-term studies that lanthanum was immunotoxic or immunosuppressive.

Reproductive toxicity
The reproductive toxicity of orally administered lanthanum carbonate was investigated in the rat in studies covering the complete reproductive cycle, including assessment of learning, behaviour and reproductive performance in F1 animals, and in the rabbit in studies of embryonic and foetal development. Systemic exposure was demonstrated in both species. Lanthanum did not pass the placenta in pregnant rats (placental transfer was not studied in rabbits). Lanthanum carbonate was not teratogenic, but some reproductive toxicity at high doses (2000 mg/kg/d to rats and 1500 mg/kg/d to rabbits), particularly with respect to delayed post-natal development, was seen. The findings in the reproductive toxicity studies are accurately reflected by the wording of section 4.6 in the SmPC.

Genotoxicity
The genotoxicity of lanthanum carbonate was studied in the standard battery of genotoxicity tests. Due to the extremely low water solubility of lanthanum carbonate and observations of tissue accumulation of lanthanum and the possible intracellular uptake of tissue-accumulated lanthanum (a prerequisite for genotoxicity), additional genotoxicity tests, more relevant to the safety evaluation, were performed. These studies included an *in vivo* micronucleus study of the water soluble chloride salt to investigate the genotoxicity of the La^{3+}-ion (the "active moiety" of lanthanum carbonate) and of UDS in rat liver after repeated i.v. dosing with lanthanum

chloride (treatment assumed to be representative of "tissue-accumulated" lanthanum as seen in repeat-dose toxicity studies). The additional *in vivo* genotoxicity tests with lanthanum chloride showed that a very high plasma level of lanthanum or a high level of tissue-accumulated (liver) lanthanum did not result in genotoxicity. There is no information on the chemical nature of tissue-accumulated lanthanum and, consequently, no information on whether lanthanum accumulated in the liver is chemically (and toxicologically) representative of lanthanum accumulated in other tissues.

Overall, the genotoxicity studies do not indicate that lanthanum carbonate is associated with any genotoxic risk.

Oncogenicity/Carcinogenicity
The carcinogenicity of orally administered lanthanum carbonate (up to 1500 mg/kg/d) was studied in conventional mouse and rat assays.

No increased incidences of malignant tumours were observed. In both mouse and rat, there was a dose-dependent increase in the incidence and severity of non-neoplastic histopathological changes in the stomach, consistent with those seen in repeated dose toxicity studies of shorter duration. In the mouse, these non-neoplastic lesions progressed to benign gastric adenoma in four high-dose males and one high-dose female. The non-neoplastic and neoplastic stomach changes in the mouse were subjected to extensive review and evaluation by several pathologists. These reviews concluded that the pathological findings in the gastro-intestinal tract of mice and rats were consistent with a local response to high doses of lanthanum carbonate. The neoplastic response in the mouse was considered to be related to an exacerbation of spontaneous pathological stomach changes in CD-1 mice. Aging CD-1 mice are predisposed to the development of spontaneous adenomatous hyperplasia and adenomatous hyperplasia was seen also in control mice. Hyperplastic lesions in treated mice showed no atypical cytological alterations suggestive of pre-malignancy. No gastric mucosal changes were seen in long-term dog studies. The positive finding only in a particularly sensitive mouse strain and negative findings in rats (hyperplasia but no tumours) and dogs (no hyperplasia) indicate that the neoplastic response in the mouse has little clinical significance.

In the first submission a small increase above historical control values in the incidence of histiocytic sarcoma in the rat was reported. In view of the hypothesis that these might be related to the activation of the lymphoreticular system by phagocytosis of systemically absorbed lanthanum present in a precipitated form, the histiocytic sarcomas were also subjected to expert pathological review and evaluation. Histiocytic sarcoma was originally reported in 5/59 high-dose males, with the haematopoietic system being the site of the primary tumour in 4/5 animals. In the 5th animal, the primary site was reported to be the liver. At re-examination, the presence of histiocytic sarcomas was confirmed in all but two of the animals. With respect to histiocytic sarcoma of haematopoietic origin, the incidence after re-examination was 3/59 (5.1%), which is slightly higher than reported historical control incidences (1.3-4%). There was no evidence of systemic activation of macrophages in lymph nodes and spleens in rats with histiocytic sarcoma. This indicates that histiocytic sarcomas in rats were of spontaneous origin rather than induced by lanthanum carbonate.

III.5 Ecotoxicity/environmental risk assessment

There are no indications that the clinical use of lanthanum carbonate as a phosphate binder would be associated with any environmental risks.

III.6 Discussion on the non-clinical aspects

Lanthanum carbonate has been demonstrated *in vitro, ex vivo* and *in vivo* to be an efficacious phosphate binder. As evident from repeated dose toxicity studies, lanthanum carbonate shows long-term efficacy with respect to phosphate binding.

The pharmacodynamically active moiety of lanthanum carbonate, the La^{3+} ion, is intended to act locally in the gastro-intestinal tract. However, animal studies with orally administered lanthanum give clear evidence that small amounts of La^{3+} ions are absorbed from the gastro-intestinal tract and accumulate in several tissues at repeated administration. Tissue accumulation at repeated dosing is an undesirable feature of a chemical substance intended to be used for medicinal purposes. The reason for the tissue accumulation of lanthanum is probably its ability to form extremely stable complexes with a large number of suitable ligands present in body fluids and tissues. Tissue accumulation and the possible toxicity that may be associated with this phenomenon was the critical issue in determining the clinical safety of lanthanum carbonate. It was concluded that, at the tissue levels seen in non-clinical studies oral lanthanum carbonate does not cause any unacceptable toxicity.

There was no evidence of lanthanum induced bone toxicity in animal studies.

Non-clinical studies did not give any evidence that orally administered lanthanum carbonate induces any hepatotoxicity in healthy rats, dogs or mice or in uraemic rats.

There was no evidence from long-term studies that lanthanum was immunotoxic or immunosuppressive.

Lanthanum carbonate was not teratogenic, but some reproductive toxicity at high doses, particularly with respect to delayed post-natal development, was seen.

Overall, the genotoxicity studies do not indicate that lanthanum carbonate is associated with any genotoxic risk.

In repeated dose toxicity studies, histopathological changes were seen in the glandular stomach of mice and rats, such as glandular hyperplasia, (sub)mucosal inflammation and squamous epithelial hyperplasia of the limiting ridge. These changes are consistent with an irritant/inflammatory response. In the mouse carcinogenicity study, a low incidence of gastric adenoma was observed at the highest dose level. The positive finding only in a mouse strain considered being particularly sensitive to development of gastric adenoma together with negative findings in rats (hyperplasia but no tumours) and dogs (no hyperplasia) indicate that the neoplastic response in the mouse has little clinical significance. No increased incidences of malignant tumours were observed.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Lanthanum is thought to act locally in the stomach, and pharmacokinetic data is mainly considered in terms of safety and interactions. Lanthanum is not metabolised. Animal studies showed that lanthanum carbonate is minimally but measurably absorbed. The human pharmacokinetic information regarding lanthanum is limited, partly due to limitations in the

bioassay. The pharmacokinetic studies were mainly conducted in healthy subjects (European and Japanese). Lanthanum is to some extent systemically absorbed, but the degree of absorption has not been evaluated. In healthy volunteers, oral administration of 3g lanthanum/day for 5 days resulted in an approximate steady state C_{max} of 0.53 ng/ml and AUC_{0-24h} of 10 ng.h/ml.

Neither a formal excretory balance study in man nor pharmacokinetic studies have been conducted in dialysis patients, but regular monitoring of plasma lanthanum was performed in the submitted studies. The mean concentrations after long-term ingestion of 3g lanthanum/day ranged from 0.5 to 0.6 ng/ml. There was no significant effect of dose or time on treatment on plasma lanthanum levels.

Food intake had a small effect on lanthanum exposure. It is recommended that lanthanum is administered at meals. Lanthanum is highly protein bound and is distributed to several organs such as bone and liver. The elimination pathways have not been determined, but a small fraction of the dose (approximately 0.00003%) is excreted renally. The elimination half-life at steady-state was estimated to be 36h at the dose 1000 mg t.i.d. The pharmacokinetics is non-linear at therapeutic doses. No interactions were observed with warfarin, digoxin or metoprolol, but interactions with orally administered drugs are theoretically possible through direct ionic interactions or through alterations in the physicochemical environment of the gastrointestinal tract lumen.

IV.3 Clinical efficacy

The product is extensively documented for a phosphate binder, including long-term data up to two years and beyond.

In all studies, lanthanum carbonate has been shown to have an effect in reducing and maintaining serum phosphate levels in patients with end stage renal disease undergoing haemodialysis or peritoneal dialysis (CAPD). A minimum starting dose of 750mg/day would be required in the majority of patients and higher starting doses should be considered in patients with higher baseline serum phosphate levels, as outlined in the SPC. Over 90% of hyperphosphataemic patients needed daily lanthanum doses of 1,500 mg or more to effectively reduce serum phosphorus levels. About two thirds of hyperphosphataemic patients were controlled on lanthanum carbonate at a daily dose up to and including 3,000mg.
Efficacy superior to that of calcium carbonate has not been demonstrated but the incidence of hypercalcaemia was much lower in the lanthanum-treated groups, with resulting benefit also for the calcium x phosphate product. This would create potential for optimised use of active vitamin D metabolites to control secondary hyperparathyroidism.

IV.4 Clinical safety

In terms of tolerability of lanthanum compared with that of calcium carbonate, similar profiles of adverse events were shown in the pivotal trials. About 70% of the adverse events in the two active treatment arms were considered to be unrelated to treatment. Gastrointestinal system disorders were the commonest adverse events across all treatment groups. In this respect, no new concern with the use of lanthanum as phosphate binder is created.

The major safety concerns discussed during evaluation related to the demonstrated gastrointestinal absorption of lanthanum and the consequent potential for tissue accumulation and damage, as signalled by non-clinical studies. The only tissue compartment available for analysis from clinical material was from iliac crest. Bone biopsy data showed clear accretion

of lanthanum, but without signs of deleterious effects on bone remodelling characteristics. The currently available bone safety data are clearly described in the SPC.

In support of the approved type II variation the MAH has provided additional pharmacokinetic data and long term data on bone morphology and lanthanum accumulation in bone.
In summary these data supports the conclusion that the bioavailability of orally administered lanthanum is very low and in the range of 0.1-0.3% without any obvious differences between healthy volunteers and ESRD patients. A slow accumulation of lanthanum in bone at comparatively low levels occurs in ESRD patients treated with conventional phosphate binders. In lanthanum treated patients considerably higher levels are observed. There seems to be some support that lanthanum is very slowly eliminated from bone after discontinuation of therapy.
The measured bone lanthanum concentrations in patients treated with lanthanum carbonate for up to 4.5 years, and the 'realistic' predicted bone concentrations after 15 years of treatment, are within the range of concentrations evaluated in life-time carcinogenicity studies in rodents.
The totality of data based on individual parameters indicates that there are no trends to indicate adverse effects on bone mineralisation, bone formation or bone resorption in patients treated with lanthanum carbonate compared to standard phosphate binder therapy. These conclusions are based mainly on paired biopsies taken after 1 and 2 years of treatment, and in a smaller number of patients after up to approximately 4.5 years treatment (n=11).
There are no indications from these results that the observed skeletal deposition of lanthanum is associated with bone toxicity of the kind observed for aluminium-containing phosphate binders.

Clinical trial data up to two years did not suggest toxicity of lanthanum to the liver, a target toxicity organ in non-clinical studies. Currently, there are no signals to indicate increased neoplastic risk.

IV.4.1 Post-marketing experience

During the latest PSUR (PSUR 3) report covering 7-Jan 2005 to 18-Sept 2005 approximately 16000 patients were estimated to have been treated with Fosrenol word-wide. No new safety signals have been identified in the post-marketing safety up-date reports, which are included in the Applicant's dossier.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Fosrenol chewable 250mg, 500 mg, 750 mg and 1,000 mg tablets is recommended for approval.

User testing of the package leaflet has been performed.

Follow-up measures

During the repeat-use procedure, some changes to the SPC were requested to be addressed in a subsequent type II variation.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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