CBG MEB

Public Assessment Report

Scientific discussion

Alfacalcidol ELC 0.25, 0.5 and 1 microgram soft capsules

(alfacalcidol)

NL/H/3772/001-003/DC

Date: 1 March 2018

This module reflects the scientific discussion for the approval of Alfacalcidol ELC 0.25, 0.5 and 1 microgram soft capsules. The procedure was finalised on 11 July 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
iPTH	intact Parathyroid Hormone
MAH	Marketing Authorisation Holder
NOAEL	No Observed Adverse Effect Level
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PTH	Parathyroid Hormone
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alfacalcidol ELC 0.25, 0.5 and 1 microgram soft capsules from ELC GROUP.

The product is indicated in conditions where there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation such as when there is reduced renal function. The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Pseudo-deficiency (D-dependent) rickets and osteomalacia
e) Hypophosphataemic vitamin D resistant rickets and osteomalacia

The product is indicated in children above 4 years, adolescents and adults.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of alfacalcidol capsules. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The product is bridged to One-Alpha capsules (alfacalcidol capsules 0.25, 0.5 and 1µg) from Leo Pharma (in the Netherland known as Etalpha LEO 0.25, 0.5 and 1 microgram with RVG license numbers 08318, 22263 and 07603). One-Alpha 0.25, 0.5 and 1 microgram capsules are registered in the Netherlands since respectively 8 January 1980, 30 August 1999 and August 1978. Given the use - as can be concluded from various guidelines - of the product since registration the application can be considered well-established.

The concerned member states (CMS) involved in this procedure were Czech Republic, Poland, Romania, Slovenia and Slovak Republic.

The marketing authorisation has been granted pursuant to article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Alfacalcidol ELC are reddish brown (0.25 microgram), light pink (0.5 microgram) or pale yellow (1 microgram) coloured, oval shaped soft gelatin capsules containing a light yellow clear oily liquid. Each capsule contains 0.25, 0.5 or 1.0 microgram alfacalcidol.

The capsules are packed in white opaque HDPE containers, with a white opaque HDPE or PP screw closure and induction sealing.

The excipients are:

Capsule fill - anhydrous citric acid (E330), all-rac-α-tocopherol (E307), propyl gallate (E310), anhydrous ethanol and refined arachis oil.
Capsule shell – gelatin (E441), glycerol (E422), sorbitol liquid partially dehydrated (E420), purified water, medium chain triglyceride, titanium dioxide (E171) and iron oxide red (0.25 and 0.5 microgram strength), black (0.25 microgram strength) and yellow (1 microgram strength) (E172).

II.2 Drug Substance

The active substance is alfacalcidol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance appears as white or almost white crystals and is practically insoluble in water, freely soluble in ethanol (96%) and soluble in fatty oils. There are no relevant polymorphism and stereo-chemical issues.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for 5 batches stored at 25°C/60%RH (6 to 9 months) and/or 5±3°C (6 to 36 months) and/or -20±3°C (6 to 36 months). Under all conditions the drug substance complies with the proposed specification, remains stable and no significant upward or downward trend for any of the tested parameters is observed. A retest period of 3 years can be granted when stored under the prescribed conditions (stored below 8°C) and provided the drug substance is kept in the original, undamaged and unopened package.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The choice of manufacturing process is justified in relation to the reference product and dosage form. The use of antioxidants and their levels is adequately justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The soft capsules are manufactured by encapsulation of the oily fill solution with gelatin shell. Process validation data on the product have been presented for 6 pilot scale and 9 full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. The specifications for the excipients are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, uniformity of fill weight, uniformity of dosage units, rupture time, disintegration time, microbial limit, active substance assay, antioxidants

assay and residual solvent. The release and shelf-life acceptance limits are very similar, except for reduced identity testing and wider limits for disintegration time and anti-oxidant assays at shelf-life. Drug product impurities are not monitored directly due to the low concentration of active substance. The proposed specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the production site have been provided on 3 pilot scaled and 3 full scaled batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 5 pilot scaled batches of each strength stored at 25°C/60% RH (12 or 24 months), 30°C/65% RH (12 or 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended HDPE container with a HDPE or PP screw closure and an induction sealing liner. Photostability studies in accordance with ICH recommendations have been performed and based on the available data, product is found to be photo stable. The claimed storage condition of "Does not require any special storage conditions" can be granted. The proposed shelf-life of 24 months and in-use shelf-life of 90 days are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alfacalcidol ELC has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Primary pharmacodynamics

Effects on bone

Oral administration of alfacalcidol in vitamin D–replete ovariectomised rats causes dose dependent suppression of osteoclastic bone resorption and stimulation of bone formation, resulting in a significant improvement in the quality as well as quantity of cortical and cancellous bone. In addition, alfacalcidol is more effective in increasing cancellous bone mass in the skeletal sites with higher bone turnover. It was also shown that alfacalcidol improved cancellous and cortical bone mass and bone strength by suppressing bone resorption and maintaining or even increasing bone formation.

Bone strength depends not only on the quantity of bone tissue but also on its quality, which is characterised by the geometry and shape of bones, the microarchitecture of the trabecular bones, the mineral deposition, and the collagen quality. In rats, alfacalcidol increases not only the amount of collagen but also enhances the maturation of collagen in ovariectomy-induced osteoporotic bones, which likely contributes to the improvement of bone quality.

A combined treatment of alfacalcidol with alendronate had a beneficial effect on the cancellous bone mass of the tibia in orchidectomised rats. In addition, bone loss induced by zonisamide could be prevented by combining zonisamide with Alfacalcidol.

Effects on muscle strength and fatigue

Glucocorticoids cause secondary osteoporosis and myopathy. In glucocorticoid-treated rats, alfacalcidol preserved bone mineral density, muscle strength and muscle volume, and prevented muscle fatigue. Furthermore, alfacalcidol increases muscle strength but does not affect muscle fatigue in ovariectomised rats. The effectiveness of activated vitamin D in preventing bone fractures may be partly owing to its effect on muscle strength in addition to its known effect on bone metabolism.

Secondary pharmacodynamics

Osteoporosis

Combination treatment of alfacalcidol and risedronate at their sub therapeutic doses can improve the mechanical properties of the spine as well as the femur and ameliorate changes in calcium metabolism in a mouse model of osteoporosis. Furthermore, alfacalcidol treatment increased cancellous and cortical bone mass and improved bone strength, resulting in the prevention of age-related bone loss in aged male rats.

Antitumor effect

In mice inoculated with sarcoma cells, alfacalcidol suppressed tumor growth or inhibited pulmonary metastases. Furthermore, Alfacalcidol has an systemic inhibitory effect on ornithine decarboxylase activity by tumour promotors.

III.2 Pharmacokinetics

Absorption and distribution

In wild type and vitamin D deficient rats, intestinal absorption following oral administration of 24(S)-3H-alfacalcidol was found to be 80% and 90%, respectively. The maximum plasma concentration of Alfacalcidol in rats was 4 hours.

In dogs, a distribution half-life of 7 hours was observed following intravenous administration of 0.2 µg/kg bw of 3H-alfacalcidol, and the maximum plasma concentration of 1, 25-dihydroxyvitamin D3 was 0.218 pmol/ml at 4 to 6 hours after dosing. Following oral administration of 0.2 µg/kg bw of 3H-alfacalcidol, plasma levels of alfacalcidol and 1,25-dihydroxy-vitamin D3 increased immediately with respective elimination half-lives (t1/2ß) of 5 and 8 hours and C_{max} values of 0.265 and 0.328 pmol/ml at 4 hours after dosing. The C_{max} of 1, 25-dihydroxy-vitamin D3 following oral dosing was higher and was achieved more rapidly than following intravenous dosing. This was attributed to significant first-pass metabolism following oral administration.

Radioactivity following oral administration of 24(S)-3H-alfacalcidol was distributed mainly to plasma, liver and small intestinal mucosa in normal and vitamin D deficient rats. Distribution to the cytosol and nuclear fractions of small intestinal mucosa were also apparent. The amount of radioactivity recovered in faeces over a period of 6 days corresponds to 39% and 49% of the administered dose after intravenous and oral dosing, respectively. A small percentage of non-volatile metabolites was excreted in urine. It is known that metabolites that resulted from the metabolism of 1,25-dihydroxy-vitamin D3 are either less potent or biologically inactive.

Metabolism

One α-Hydroxyvitamin D3 (1(OH) D3) is a synthetic prohormone that can be converted to 1α, 25-dihydroxyvitamin D3 (1, 25(OH)2D3), the biologically active form of vitamin D3. This conversion occurs in the liver by the 25-hydroxylase activities of CYP3A4, CYP2J2, CYP27A1 and CYP2R1.

III.3 Toxicology

Repeat-dose toxicity

Several oral repeated-dose toxicity studies (ranging from one to twelve months) were performed in rats and dogs. Key studies are summarised below:

Rat

In a one month study in rat, mortality, inhibited bodyweight gain, moderate leukocytosis, increased plasma calcium, total protein, total cholesterol, blood-urea nitrogen, and proteinuria occurred at doses of 12.5 µg/kg bw or higher. The No Observed Adverse Effect Level (NOAEL) in this study was 0.5 µg/kg bw.

In a three month study in rat, deaths occurred at 2.5 and 5 µg/kg bw. At doses of 0.1 µg/kg bw or higher effects observed included decreases of erythrocyte, leukocyte, lymphocytes, serum protein, albumin, glucose and potassium while neutrophils, serum and urinary calcium increased. Ectopic calcification typical of hypercalcaemia was present in kidney and heart.

In a six month study in rats, bodyweight gain and food intake were decreased at 0.5 µg/kg bw/day and higher. An increase in serum and urinary calcium and inorganic phosphorus were present at doses of 0.1 µg/kg bw/day and higher. Histopathological studies revealed renal tubular degeneration,

degeneration of cardiac muscle and blood vessel walls, atrophy of the medulla in the thymus gland and calcification of gastro-intestinal mucosa. The NOAEL in this study was 0.02 µg/kg bw/day.

Dog
In a one month study in dog, at 1 µg/kg bw/day and higher, bodyweight, food intake, and lymphocytes were decreased, while urinary and plasma calcium concentrations, glutamicoxaloacetic transaminase, alkaline phosphatase, blood-urea nitrogen, total bilirubin and neutrophils were increased. Necropsy findings included hydrothorax, pulmonary oedema, cardiac muscle degeneration, white discoloration in kidney and gastro-intestinal tract, intestinal haemorrhage and atrophy of the thymus and reproductive organs. The NOAEL was considered to be 0.04 µg/kg bw/day.
In a one year dog study, 0.08 µg/kg bw/day revealed reduced weight gain and food intake, ataxia, and emaciation, as well as a decrease in haematocrit, haemoglobin and erythrocyte counts. Increased serum calcium and inorganic phosphorus and blood-urea nitrogen were present. There were also effects on phenolsulphonphthalein excretion and glomerular filtration rate in the same dosage group. Histological changes (calcium deposition in the cavity and on the epithelial cells of renal tubules and atrophy of thymus cortex and medulla) were also observed in the 0.08 µg/kg bw/day group. The NOAEL was 0.02 µg/kg bw/day.

Carcinogenicity
The MAH did not provide a study or a statement on carcinogenicity

Genotoxicity
The potential to induce reverse mutations in Salmonella typhimurium strains (TA98, TA100, TA1535, TA1538 and TA1537) was examined using the spot test and plate incorporation methods devised by Ames. Solutions in dimethyl-sulfoxide of 0.25 to 250 µg/plate were applied in the spot test and 250 µg/plate was found to represent the limit of solubility in the plate incorporation method. There were no increases in the numbers of revertant colonies, either in the presence or absence of metabolic activation.
The potential of alfacalcidol to induce forward mutations at the thymidine kinase locus in cultured mouse lymphoma L5178Y cells in the absence and in the presence of metabolic activation was assessed. Alfacalcidol did not induce any dose-related or statistically significant increases in the frequency of mutant colonies.

Reproductive toxicity
Embryo fetal toxicity studies were performed in rat and rabbit.
In rat a reduction in maternal weight was observed at doses of 0.5 µg/kg bw/day and higher. At 2.5 µg/kg bw/day, increased intra-uterine death and fetal growth retardation including reduced ossification occurred secondary to severe maternal toxicity.
In rabbit, maternal toxicity included diarrhoea, reduced feces and reduced body weight gain at all but the lowest dose tested (0.08-0.5 µg/kg bw/day). At all but the lowest dose fetal resorptions were increased and there was a dose dependent increase in number of abortions. The fetal NOAEL in rabbits was 0.02 µg/kg bw/day.

Immunotoxicity
Tests for active and passive cutaneous anaphylaxis were negative up to 0.5 µg/kg bw in guinea pigs.

III.4 Ecotoxicity/environmental risk assessment (ERA)

It is expected that Alfacalcidol ELC will be a substitution for other products on the market and the use of Alfacalcidol will not increase. Based on this assumption, an ERA is not warranted.

III.5 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of alfacalcidol are well known. As alfacalcidol is a widely used, well-known active substance. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Alfacalcidol is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The pharmacokinetics of alfacalcidol, is although limited, considered sufficiently supported by literature data. Alfacalcidol can be used when there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation such as when there is reduced renal function. Alfacalcidol is absorbed passively and almost completely in the small intestine. Alfacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin D3. This is the metabolite of vitamin D which acts as a regulator of calcium and phosphate metabolism. The half-life of alfacalcidol is about 4 hours.

For the purpose of bridging the literature data to the proposed formulation, the MAH selected One-Alpha and AlfaD 0.25 mcg, 0.5 mcg and 1.0 mcg soft capsules marketed by Teva UK Limited (UK MA-numbers: PL 00289/0459, 0460, 0461 since 25 January 2002, 6 November 2001 and 25 January 2002 respectively) as reference product to substantiate the bridging to the literature data. As indicated, the lipid soluble alfacalcidol is dissolved in oil in the test formulation and the 2 reference formulations. In the test formulation arachis oil is used, which is the same oil as used in the reference AlfaD. In One Alpha alfacalcidol is dissolved in sesame oil. The influence of the different oil has no effect on the absorption of alfacalcidol, as shown by a bioequivalence study between One Alpha and a capsule formulation comparable to the test formulation (same quantitative composition with arachis oil). The test and AlfaD reference formulation have the same qualitative composition, but qualitatively this is not known, due to lack of information for the reference formulation.

As dissolution data with an oily solution is not useful, disintegration data are submitted to further support the bridge. These data did not show consistent results, i.e. test formulation shows faster, slower or comparable disintegration times depending on strength and batch used. However, the data also show that the observed difference in disintegration time is small and it is expected that this will not affect clinically relevant the absorption of alfacalcidol.
Based upon the fact that the test and reference formulations contain alfacalcidol in an oily solution, the comparability in composition of the test and reference formulations, the data from the bioequivalence study showing no effect of a sesame oil instead of arachis oil on the absorption of alfacalcidol and the disintegration time, a comparable absorption of alfacalcidol is expected between the test and selected reference formulations.

The MAH submitted 44 literature references supporting pharmacokinetics, pharmacodynamics, efficacy and safety. Detailed search in the used products revealed that 6 refer to One Alpha, 4 publications refer to AlfaD, 2 refer to Etalpha (oily solution in capsule also from Leo Pharma), and in 4 other also oily solutions were used. This means that in at least 16 cases an oily solution was used (36%). Moreover in at least 8 additional cases a Leo Pharm calcitriol formulation was used, but it cannot be confirmed if this was the reference oily solution. Therefore, considering that in at least 36% an oily solution has been used not only to support the pharmacokinetics but also the pharmacodynamics, efficacy and safety, and considering that the product it self is a solution for which normally a bioequivalence study can be waived, this is acceptable..

IV.3 Pharmacodynamics

Alfacalcidol exerts its primary pharmacodynamic action upon hydroxylation of the pro-drug in the liver, resulting in the formation of calcitriol which is the active form of vitamin D. Reduced endogenous calcitriol levels as observed in chronic kidney disease (CKD) patients contribute to the development of renal osteodystrophy and in particular the evolution of secondary hyperparathyroidism. Supplementation of calcitriol by vitamin D analogues is common clinical practice in CKD patients throughout the world. Alfacalcidol belongs to one of the initial vitamin D analogues used and has a

long history of use (since 1978). The effects of alfacalcidol can be easily understood from the actions of endogenous calcitriol. Due to its secondary effects on calcium and phosphate absorption (increased absorption), serum calcium and phosphate levels should be monitored regularly. In addition, to avoid a too low serum parathyroid hormone (PTH) and the development of a dynamic bone disease with low bone turnover, serum parathyroid hormone levels must be monitored regularly as well.

IV.4 Clinical efficacy

The following indications were claimed by the MAH:
- Renal osteodystrophy
- Hyperparathyroidism (with bone disease)
- Hypoparathyroidism
- Neonatal hypocalcaemia
- Nutritional and malabsorptive rickets and osteomalacia
- Pseudo-deficiency (D-dependent) rickets and osteomalacia

No comments were raised in the initial assessment round to the first two indications (renal osteodystrophy and hyperparathyroidism (with bone disease)). For the remaining indications a major concern was forwarded. Based on the submitted literature the following indications were also approved:
- Hypoparathyroidism
- hypophosphataemic osteomalacia/rickets
- Pseudo-deficiency (D-dependent) rickets and osteomalacia

The indications neonatal hypocalcaemia Nutritional and malabsorptive rickets and osteomalacia were not acceptable and were deleted during the procedure.

Some studies with alternative dosing (iv versus oral or continues vs pulse vs intermittent) were included in the MAA. The used doses varied from 0.25 to 2 µg. No clear conclusions could be derived from the more or less anecdotal references.
The dosing regimen is derived from the European reference product One-Alpha. Further the dosing regimen is in line with current standard clinical practice. Given the vast experience with alfacalcidol no further information is deemed necessary.

From the submitted studies can be learned that in CKD patients pre-dialysis or on haemodialysis, alfacalcidol orally once daily reduced intact parathyroid hormone (iPTH) levels in the majority of the patients. The high proportion (about 80%) of patients with at least a 30% reduction of iPTH indicates that alfacalcidol is effective in lowering iPTH levels supporting its well-known use in the treatment of secondary hyperparathyroidism. In a post-hoc analysis a total of 82 out of 142 patients had iPTH levels above 33 pmol/l at baseline. Upon treatment (any dosing regimen) 63 out of 82 patients had iPTH levels below 33 pmol/l, indicating that about 75% of the patients currently considered for treatment reached levels below the upper target level further supporting the efficacy of the active treatment.
Based on the submitted literature it can be concluded that alfacalcidol can be used in (pre-)dialysis patients to correct disturbance of calcium metabolism when there is reduced renal function. This results in the preservation of bone mass in the (pre-)dialysis patients. As renal osteodystrophy and secondary hyperparathyroidism (with or without bone disease) are also manifestations of a decline in renal function the beneficial effects of alfacalcidol in these patients is also reported in the various studies submitted.

IV.5 Clinical safety

The most frequently reported undesirable effects are hypercalcaemia (rare) and various skin reactions (very rare). Also rarely reported were renal impairment, nephrocalcinosis, pruritus, rash, urticaria.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alfacalciferol treatment may then be re-started at half the previous dose.
In the case of renal impairment, elevated serum phosphate levels may be induced by Alfacalcidol therapy. The dosage should be adjusted to the patient's requirements.

Adverse events reported in clinical trials
In several clinical trials, it was found that hypercalcaemia occurred more often among patients given alfacalcidol. Hypercalcaemic episodes were readily reversible by decreasing the daily dose of alfacalcidol or the hypercalcemia disappeared in every case within 48 hours after discontinuing the administration of the drug. The undesirable effects and adverse events reported in the clinical trials are considered adequately discussed and therefore accepted.

Post-marketing surveillance studies
In a post marketing surveillance (PMS) of almost 2,000 dialysis patients with renal osteopathy, the course of therapy with alfacalcidol (Bondiol) was observed over a 6-month period. In 55.9% of cases, alfacalcidol was administered orally at a daily dose of 0.25 microgram. In 26.6% of patients, alfacalcidol was administered every second day at a dose of 0.25-1 microgram/day. In 16.1% of patients, alfacalcidol was administered as pulse-therapy, mostly at a dose of 1-2 microgram once or twice per week. The tolerability of the alfacalcidol treatment was evaluated “good” to “very good” by the treating physicians in 93% of the cases. Possible or certain adverse events (AE) in association with the alfacalcidol treatment occurred in 7 of the 1945 patients (0.4%). These AEs included nausea and constipation as well as heartburn, dizziness, itching, erythema and a suspected parathyroid gland adenoma with an increased PTH. Based on the result, it was concluded that alfacalcidol is a highly safe therapy of renal bone disease.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alfacalcidol ELC.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypercalcaemia - Hyperphosphataemia - Skin reaction - Acute kidney failure
Important potential risks	- Arrhythmia due to interaction with cardiac glycosides or digitalis - Calcinosis
Missing information	- Use in pregnancy - Use during lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, no new clinical studies were conducted. The MAH provided a clinical overview, covering 44 publications up to the year 2016. Bridging to literature data had been sufficient supported, as well as pharmacokinetics, pharmacodynamics, efficacy and safety. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. A total of 20 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alfacalcidol ELC 0.25, 0.5 and 1 microgram soft capsules have a proven chemical-pharmaceutical quality. Alfacalcidol ELC is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Alfacalcidol ELC with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 11 July 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse