CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Etalpha LEO 0.25, 0.5 and 1 microgram, capsules, soft
LEO Pharma B.V., the Netherlands

alfacalcidol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1928/001-003/MR
Registration number in the Netherlands: RVG 08318, 22263, 07603

26 August 2010

Pharmacotherapeutic group:	vitamin D and analogues
ATC code:	A11CC03
Route of administration:	oral
Therapeutic indication:	prevention and treatment of renal osteodystrophy and treatment of secondary hyperparathyroidism in patients with chronic kidney disease stage 3-5.
Prescription status:	prescription only
Date of first authorisation in NL:	0.25 µg – 8 January 1980 0.5 µg – 30 August 1999 1 µg – 4 August 1978
Concerned Member States:	Mutual recognition procedure with ES, PL, RO
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Etalpha LEO 0.25, 0.5 and 1 microgram, capsules, soft, from LEO Pharma B.V. The date of authorisation in the Netherlands was on 4 August 1978 for the 1 µg capsules, followed by 0.25 µg on 8 January 1980 and 0.5 µg on 30 August 1999.

The product is indicated for prevention and treatment of renal osteodystrophy and treatment of secondary hyperparathyroidism in patients with chronic kidney disease stage 3-5.

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

Alfacalcidol (1α-hydroxy vitamin D3, 1α(OH)D3), the active substance in One-Alpha®, is a synthetic vitamin D analogue. Alfacalcidol is a pro-drug that exerts its action after it has been metabolised to calcitriol (1α,25(OH)2D3), mainly in the liver. Calcitriol is the physiologically active form of vitamin D hormone, and under normal circumstances calcitriol is formed primarily in the kidney by a 1α-hydroxylase-mediated enzymatic hydroxylation of calcifediol (25(OH)D3). As a consequence of the presence of the 1α-hydroxyl group, alfacalcidol only requires hydroxylation at the 25 position in the liver to yield calcitriol and therefore acts independently of renal function.
In patients with chronic kidney disease, impaired 1a-hydroxylation by the kidneys reduces endogenous calcitriol production. This contributes to the disturbances in bone and mineral metabolism including secondary hyperparathyroidism and renal bone disease. Calcitriol has direct effects on the parathyroid gland to prevent parathyroid gland hyperplasia and also has additive effect with calcium to suppress PTH production. Calcitriol also increases gastrointestinal absorption of calcium to correct hypocalcaemia. Calcitriol directly affects osteoblasts in bone and may lead to improved bone formation and mineralization

LEO Pharmaceutical Products Ltd. A/S started research in the vitamin D area in 1973 and alfacalcidol was synthesised. Concurrently, researchers in the United States had produced alfacalcidol. A license agreement was signed where LEO Pharma got the rights to the product in most of the world. The original approval of Etalpha capsules in 1978 was based on data from clinical studies available at that time. The product is also registered in several countries as One-Alpha® capsules.

This mutual recognition procedure concerns the original full application for Etalpha, made in 1978 in the Netherlands for the 1 µg capsules and the subsequent authorisations for the 0.25 and 0.5 µg capsules.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application is based on a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. The quality assessment of the medicinal product is discussed in chapter II of this report.
In support of the efficacy and safety of the product in the proposed indications, the MAH submitted a number of clinical studies:

- 3 pharmacokinetic studies (a bioavailability study to investigate food interaction, a bioavailability study to investigate the relative bioavailability of the alfacalcidol capsules and a bioavailability study to evaluate the pharmacokinetic profile of alfacalcidol and its main metabolite).
- four studies in patients with renal failure (OA 186, OA 0301 DE, OA 187, and UA 190 F).

In addition, four studies in other indications were submitted, but considered irrelevant and therefore these were not assessed.
Besides safety data obtained from the clinical studies, post-marketing surveillance data were assessed in order to establish the safety profile of the product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this was not required at the time of the initial application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is alfacalcidol, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Alfacalcidol is a white, crystalline powder. The active substance is practically insoluble in water, freely soluble in ethanol and slightly soluble in propylene glycol and sesame oil.

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 new 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 MAH adopted Ph.Eur. specifications and analytical methods, as well as the additional specifications/ analytical methods as included on the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four production-scale batches.

Stability of drug substance
The re-test period for the drug substance is three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Etalpha LEO 0.25 microgram are cream coloured and egg-shaped soft gelatin capsules.
Etalpha LEO 0.5 microgram are red and egg-shaped soft gelatin capsules.
Etalpha LEO 1 microgram are brown and egg-shaped soft gelatin capsules

The soft capsules are packed in blister packaging consisting of a white non-transparent aluminium push-through foil and a PVC blister film, covered with a non-transparent aluminium laminate lidding

The excipients are:

Capsule content
sesame oil, refined
all-*rac*-α-Tocopherol (E307)

Capsule shell
gelatin

glycerol (E422)
potassium sorbate (E202)
titanium dioxide (E171) (*0.25 and 0.5 µg only*)
Red iron oxide (E172) (*0.5 and 1 µg only*)
Black iron oxide (E172) (*1 µg only*)

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Solutions of alfacalcidol in sesame oil are relatively stable. The solubility in alfacalcidol is over 350 times the concentration to be encapsulated.
For the antioxidant and preservative used proof of safety and efficacy, a method of control and level of preservative/antioxidant of the opened and unopened container during storage are advised to be included.
The pharmaceutical development of the product has been adequately described.

Manufacturing process
The manufacturing process consists of dissolution, after which the mass is stirred, filtered, mixed and encapsulated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for production-scale batches of each strength.

Control of excipients
Except for the iron oxides, the excipients comply with the Ph.Eur. The iron oxide complies with Directive 95/45/EC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, uniformity of mass, disintegration and microbial purity. Except for the lower limit for assay alfacalcidol and all-rac-α-tocopherol, the release and shelf-life requirements are identical. Purity tests have not been performed, since a test cannot be developed, due to the low dose and interference of the sesame oil. As requested, the MAH included a requirement for identification of colourants.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 18 recent production-scale batches stored at 25°C/60% RH (6-24 months) and 30°/65% RH (13 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 opaque PVC-Alu blisters
At long term storage conditions a decrease in assay of alfacalcidol has been observed. A decrease in the content of all-rac-α-tocopherol has also been observed. Although no significant changes have been observed at intermediate and accelerated conditions, the storage condition ‘store below 25ºC’ is justified by the results at long term storage conditions and the extreme sensitivity of the drug substance.
A photostability study according to ICH conditions has been performed, indicating that the drug product is stable with respect to light. Based on the stability data provided, the claimed shelf-life could be granted: 24 months when stored below 25ºC.

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.2 Non clinical aspects

Etalpha LEO formulations contain a well-known active ingredient, alfacalcidol (1α-hydroxy vitamin D3), with long term human market experience. The pharmacodynamics, pharmacokinetics and toxicology of alfacalcidol are well known. The non-clinical studies show a non-clinical safety profile that is consistent with the pharmacological mechanism of action, and what is known clinically for alfacalcidol. The toxicity of alfacalcidol is attributed to the known vitamin D-effect of calcitriol on calcium homeostasis, which is characterised by hypercalcaemia, hypercalciuria and eventually soft tissue calcification. Furthermore, the risk assessment supports the oral and i.v. systemic safety of Etalpha LEO formulations in man, for the prescribed use in treatment of secondary hyperparathyroidism in patients with chronic kidney disease.

Environmental risk assessment
An Environmental Risk Assessment (ERA) for One-Alpha is not necessary since the active ingredient is a pro-drug for a vitamin and vitamins are exempted from the need for an ERA. Nevertheless, the MAH has provided an accetable ERA, which has been assessed.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The clinical studies OA 0403 CA, OA 0401 CA, OA 0402 DE, and OA 0301 DE were conducted in compliance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP). Studies OA 186, OA 187, and UA 190 F were conducted between 1986 and 1990. These studies were conducted in accordance with the guidelines of that time.

Pharmacokinetics
Regarding pharmacokinetics, 3 studies have been submitted: study OA 0403 CA (a bioavailability study to investigate food interaction), study OA 0401 CA (a bioavailability study to investigate the relative bioavailability of the Etalpha LEO alfacalcidol capsules (0.25, 0.5 and 1µg)) and study OA 0402 DE (a bioavailability study to evaluate the pharmacokinetic profile of alfacalcidol (1α-hydroxyvitamin D3) and its main metabolite 1.25-dihydroxyvitamin D3). The results of these studies are presented below.
In addition, a short review on the well known pharmacokinetics of alfacalcidol is included. Alfacalcidol is a well-known active ingredient with long term human market experience. Also, the pharmacokinetic profile of alfacalcidol has been widely recognized.

Study OA 0403 CA: food effect and absolute bioavailability of the capsules
Design
This was a bioavailability study to investigate food interaction with a single dose of alfacalcidol (1α-hydroxyvitamin D3): a comparative, open-label, randomized, single-dose, 3-way crossover, food effect and absolute bioavailability study of Etalpha LEO alfacalcidol following a dose of 10 µg in healthy adult volunteers. The study population consisted of a total of 18 subjects (14 males and 4 females). Each subject received on three different occasions, according to a randomization scheme:
(A) a single 10 µg dose of alfacacidol capsule under fasting conditions
(B) a single 10 µg dose of alfacacidol capsule under fed conditions (standard high-fat breakfast consisting of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk, 30 minutes prior to dosing)
(C) a 10 µg dose of alfacacidol solution as an iv infusion of 5 minutes under fasting conditions.

The washout period was 21 days. Blood samples were taken at –46h, -24h, pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 36, 48, 72, 96, 120, and 144 hours post-dose. In addition, for subjects randomized to Treatment C, blood was also drawn at 0.133 (3 minutes following the end of the infusion time).
Statistical and calcitriol pharmacokinetic analyses were performed on data collected from 18 subjects following oral and iv alfacalcidol administration. Statistical and alfacalcidol pharmacokinetic analyses following iv administration were performed on data collected from 18 subjects.

Results

Figure PK 1. Mean (CV%) unadjusted alfacalcidol pharmacokinetic parameters when administered as a capsule under fasted and fed conditions and as an iv infusion

	A (fasted)	B (fed)	C (*iv* infusion)
AUC 0-t* (pg·h/mL)	321 (33.9) (n= 9)	425 (52.0) (n = 13)	1442 (26.1) (n = 18)
AUCinf* (pg·h/mL)	-	1105 (42.0) (n = 3)	1750 (22.7) (n = 17)
Cmax (pg/mL)*	75.0 (15.4) (n = 9)	94.8 (23.0) (n = 13)	1785 (35.1) (n = 18)
tmax (h)	6.44 (13.7)	5.54 (26.2)	0.0833**
kel (1/h)	-	0.147 (28.2)	0.197 (47.8)
$t_{1/2}$ (h)	-	5.02 (31.6)	4.30 (43.4)
CL (L/h)	-	-	5.85 (22.9)
F (%)	20.9 (40.4)	-	-

*Geometric means are represented for these parameters

**Simulated concentration at 0.0833 h when infusion stopped

Figure PK 2. Mean (CV%) baseline-adjusted calcitriol pharmacokinetic parameters following alfacalcidol administration as a capsule under fasted and fed conditions and as an iv infusion (n = 18)

	A (fasted)	B (fed)	C (*iv* infusion)
AUC 0-48 (pg·h/mL)*	1693 (46.1)	1533 (51.7)	1519 (49.2)
AUCinf (pg·h/mL)*	1629 (74.0) (n = 17)	1485 (65.2) (n = 15)	1862 (64.6) (n = 14)
Cmax (pg/mL)*	93.3 (27.3)	71.4 (28.8)	67.7 (43.8)
tmax (h)	7.56 (33.1)	13.7 (54.3)	6.51 (35.4)
kel (1/h)	0.0900 (32.2)	0.0802 (59.7)	0.0568 (81.9)
$t_{1/2}$ (h)	8.71 (40.6)	10.5 (40.1)	18.3 (54.6)
CL/Fm (L/h)	-	-	6.36 (64.2)

*Geometric means are represented for these parameters

Figure PK 3. Ratios of LSM (90% Confidence Intervals).

Parameter	Alfacalcidol Fasting (A) vs. Fed (B) (n = 7)	Adjusted Calcitriol Fasting (A) vs. Fed (B) (n = 18)
AUC 0-t	63.2% (43.8%-91.2%)	-
AUC 0-48	-	110.4% (90.8%-134.2%)
AUCinf	-	96.2% (70.0%-132.3%) (n = 14)
Cmax	76.7% (56.7%-103.9%)	130.7% (114.3%-149.5%)

Conclusion
Like vitamin D3, alfacalcidol is highly lipophilic. Food increased bioavailability possibly by enhanced transport via the lymphatic route. In addition, first pass metabolism can be by passed, and metabolism delayed, which may explain the late tmax under fed conditions. However, the result for alfacalcidol should be interpreted with caution, as after oral dosing, the plasma levels were just above the limit of detection and in general limited data points could be taken into account to describe the pharmacokinetics.
The SPC states that the capsule can be taken with or without food, which is agreed.

Study OA 0401 CA: Bioavailability capsules and oral drops
Design
This was a bioavailability study to investigate the relative bioavailability of Etalpha LEO alfacalcidol (One-Alpha®) capsules (0.25, 0.5 and 1µg) and the oral drops (One-Alpha® 2µg/ml) following a dose of 10 µg in healthy adult volunteers. The 0.25 µg is considered the reference product.
The study population consisted of a total of 72 subjects (43 males and 29 females). Each subject received on 4 different occasions, according to a randomization scheme:
(A) a single 10 µg dose of 0.25 µg alfacacidol capsule under fasting conditions
(B) a single 10 µg dose as 0.5 µg alfacacidol capsules under fasting conditions
(C) a single 10 µg dose as 1 µg alfacacidol capsules under fasting conditions
(D) a single 10 µg dose as oral solution under fasting conditions

The washout period was 14 days.
Blood samples were taken at -46h, -24h, predose and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36 and 48 hours post-dose. Alfacalcidol was not measured due to analytical limitations. Calcitriol in serum was analyzed using a validated methods.

Results
The mean t_{max} values for baseline unadjusted calcitriol ranged from 7 to 8 hours following a 10 µg dose of alfacalcidol administered as capsules or oral drops.

Figure PK 4. Summary of geometric mean pharmacokinetic parameters (CV%) for baseline adjusted calcitriol.

Treatment	AUC 0-t (pg.h/mL)	AUCinf (pg.h/mL)	Cmax (pg/mL)
A	1931 (46.8%) n=70	2184 (42.1%) n=68	108 (29.2%) n=70
B	1996 (49.3%) n=70	2259 (45.1%) n=64	113 (34.2%) n=70
C	2067 (46.2%) n=66	2220 (47.3%) n=60	118 (27.5%) n=66
D	2320 (31.8%) n=69	2529 (28.7%) n=65	130 (21.9%) n=69
Comparisons of Interest: Ratios of LSM (90% Confidence intervals)			
B vs A	103.0% (94.8% – 112.0%)	101.3% (93.7% – 109.4%)	104.2 (99.7% – 108.9%)
C vs A	108.4% (99.5% – 118.1%)	101.5% (93.7% – 109.9%)	110.0 (105.2% – 115.1%)
D vs A	120.8% (111.0% – 131.3%)	115.4 (106.8% – 124.6%)	121.2% (115.9% – 126.7%)

Conclusion
Based upon the baseline unadjusted data, the 0.5 and 1 µg capsules and the oral drops are bioequivalent to the 0.25 µg capsule. Based upon baseline adjusted data, the 0.5 and 1 µg capsules are bioequivalent to the 0.25 µg capsule. For the oral drops an increase in bioavailability is observed, leading to 90% CI outside the 80-125% interval, but still within the 75 – 133% interval. This difference is considered not clinical relevant. Moreover, the drops are not included in the MRP at issue.

Study OA 0402 DE: Multiple dose study in patients with chronic renal failure undergoing haemodialysis
Design
This was a bioavailability study to evaluate the pharmacokinetic profile of alfacalcidol (1α-hydroxyvitamin D3) and its main metabolite 1.25-dihydroxyvitamin D3 after repeated doses (pulse dose regimen) of alfacalcidol (capsule) in patients with chronic renal failure undergoing haemodialysis. During the trial, dialysis sessions lasting from 3 to 8 hours were performed three times a week with intervals of 48 or 72 hours. All patients entered a two-week washout period before the treatment started. During the treatment phase, patients received a 1.5 µg oral dose of alfacalcidol (6 × 0.25 µg) three times a week for two weeks at the end of their regular dialysis sessions (visit days 3 - 8). Blood samples for the pharmacokinetic analysis were obtained over the 72 hours after the last dose of the two-week treatment phase. 14 subjects were included and 12 subjects completed the study.
Alfacalcidol was not measured due to analytical limitations. Calcitriol in serum was analyzed using a validated method.

Results
Figure PK 5. Mean steady state calcitrol pharmacokinetic values in patients with chronic renal failure undergoing haemodialysis.

	AUC[a] pg·h/ml	AUC_{inf} pg·h/ml	AUC/AUC_{inf} %	C_{max} pg/ml	T_{max} h	$t_{½}$ h
Baseline unadjusted calcitriol	2036 (58.5%)	NA	NA	54.4 (46.8%)	9.42 (41.1%)	NA
Baseline adjusted calcitriol	630 (49.0%)	967 (37.0%)	72.2 (21.7%)	34.3 (43.4%)	9.42 (41.1%)	19.2 (29.7%)

[a]AUC corresponds to AUC_{0-t} for unadjusted concentrations and AUC_{0-48} for baseline adjusted concentrations

NA: not applicable. N = 12

Results

After a washout period, during which treatments with vitamin D or any vitamin D analogue were prohibited, mean pre-treatment concentrations of calcitriol (-336 hours) in patients with chronic renal failure were below the endogenous levels reported in the literature in healthy subjects. At the end of the last dialysis sessions of the treatment period (0 hour), predose concentrations were similar to pre-treatment concentrations, suggesting no apparent accumulation of the drug following multiple oral administrations of alfacalcidol in patients with chronic renal failure undergoing haemodialysis.

Mean concentration profiles of calcitriol were characterized by two absorption peaks. The second peak occurred at approximately 12 hours and may be attributed to enterohepatic recycling of the drug.

Applying a dose scheme of 1.5 µg oral dose of alfacalcidol (6 × 0.25 µg) three times a week for two weeks at the end of their regular dialysis sessions resulted in calcitrol plasma concentrations in the range observed for healthy subjects. Moreover, no accumulation of the drug following repeated oral administrations of alfacalcidol is observed. This study sufficiently supports the dosage advice in this patient group.

Pharmacodynamics

No human pharmacodynamic studies were included in the current application, which is acceptable.

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 CKD patients contribute to the development of renal osteodystrophy and in particular the evolution of secondary hyperparathyroidism. Supplementation of calcitriol by vitamin D analogs is common clinical practice in CKD patients throughout the world. Alfacalcidol belongs to one of the initial vitamin D analogs 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 PTH and the development of adynamic bone disease with low bone turnover, serum PTH levels must be monitored regularly as well.

Clinical efficacy

The MAH submitted four clinical studies performed after the initial application in 1978 in support of the current indication and posology. Study OA 186 (1989-1991) is considered the pivotal study for the efficacy in prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism in pre-dialysis patients whereas study OA 0301 DE (2003-2004) is considered the pivotal study for use in haemodialysis patients (CKD stage 5). Studies OA 187 and UA 190 F were open label studies conducted between 1986 and 1991 and are considered supportive data for the solution for injection.

Study OA 186

Design

This was a phase 3 multi-centre, double-blind, placebo-controlled, parallel group study designed to demonstrate the prevention of histological abnormalities in bone and development of hyperparathyroidism in pre-dialysis patients with early chronic renal failure.

Patients aged ≥ 18 years, of either sex, with chronic renal failure (creatinine clearance 15-50 ml/min) were included in this study. Major exclusion criteria included significant hepatic diseases, a high probability of dialysis treatment within the next three months, treatment with high doses of vitamin D or vitamin D metabolites in the past 6 months, hypercalcaemia, and bone disease (symptomatic, radiographic or serum alkaline phosphatase levels above normal).

After a qualification phase lasting up to 1 month during which laboratory parameters including creatinine clearance were checked, patients entered a dose titration phase of 4 months during which the dose of the assigned medication was titrated according to serum calcium levels. Patients received One-Alpha® capsules for oral use as a single dose with food each morning. The initial dose was 0.25 µg/day. If hypercalcaemia occurred the dose was reduced to 0.25 µg on alternate days. After the first four months, patients entered a maintenance phase of 20 months during which maintenance treatment was continued. The maximum dose was 1 µg/day.
All medication for other conditions than bone disease of hyperparathydoidism was allowed. Calcium supplements were to remain stable. Phosphate-binding agents (other than calcium carbonate) were given when dietary measures failed to maintain adequate serum phosphate levels. Dietary measures were not standardised but each centre followed normal dietary policy.

The objectives were to determine:
1. the efficacy of alfalcalcidol during early chronic renal failure in:
    a. the prevention of the development of histological abnormalities in bone and
    b. the prevention of the development of hyperparathyroidism.
2. the safety of alafacalcidol during early chronic renal failure.
3. the effect of alafacalcidol on the rate of decline of renal function in early chronic renal failure.

Primary efficacy endpoint
The primary response criterion was the incidence of bone abnormality at the end of the trial (2 years or upon early withdrawal). Bone abnormalities were assessed as the presence of one or both of the following:
1. Osteomalacia, defined as the presence of 5 or more osteoid lamellae visible under polarised light in any a osteoid seam.
2. Osteitis fibrosa, defined as the presence of at least grade 2 osteitis fibrosa (grade 2: fibrosis present on resorbing surfaces of the osteoid surfaces).

Secondary efficacy endpoint
1. Changes in serum levels of iPTH from baseline to the end of the trial were assessed.
2. Changes in creatinine clearance rates from baseline to 6, 12, 18 and 24 months were compared for the two groups.

Other parameters assessed were changes in quantitative histomorphometric parameters, grading of the extent of bone pain and myopathy, grading of sub-periosteal erosions of the hand and clavicle. In addition, the change from baseline to end of trial in serum alkaline phosphatase and $1,25(OH)_2D_3$ were assessed.

Results
A total of 179 patients were enrolled in the study at 17 centres in Europe of which 177 were randomised to treatment. A total of 39 (22%) out of 177 randomised patients were withdrawn from double-blind treatment; 16 (18%) in the alfacalcidol treated group and 23 (26%) in the placebo-treated group. The most common reason for withdrawal was patients requiring dialysis (n=8 (9.0%) in the alfacalcidol treated group and n=10 (11.4%) in the placebo-treated group). Four patients died in the alfacalcidol treated group and one in the placebo-treated group. Patients that died in the alfacalcidol treated group died because of underlying co-morbidity (a cerebrovascular accident, an acute myocardial infarction, cardiac failure and lung carcinoma). The patient in the placebo group died at home with cause of death unknown.
Other reasons for withdrawal in the alfacalcidol treated group were defaulted (n=2), nephrectomy (n=1), and exclusion criteria emerging (n=1). Other reasons for withdrawal in the placebo group were moved away (n=2), drug supplies past expiry date (n=1), hypertensive encephalopathy (n=1) and persistent hypocalcaemia (n=1).

The mean treatment duration was 92 weeks (range 4 – 122 weeks) in the alfacalcidol treated group and 89 weeks (range 5-112 weeks) in the placebo-treated group. Over 90% of patients included in the primary analysis had a treatment duration of at least 90 weeks.
All patients started at a dose level of 0.25 µg/day. At the last visit when treatment was prescribed, 45.5% of the patients received 0.25 µg/day, 30.3% 0.5 µg/day and 11.9% 1 µg/day. The mean maintenance dose was 0.43 µg/day.

Primary efficacy analysis
Of the 89 patients randomised to treatment with alfacalcidol, 72 provided both baseline and end of treatment biopsies. In the placebo treated group, 62 out of 87 patients had both baseline and end of treatment biopsies available. The number of patients with bone abnormality present at baseline was 76.4% in the alfacalcidol treated group and 72.6% in the placebo treated group. At the end of treatment, 54.2% of the alfacalcidol treated patients versus 82.3% of the placebo-treated patients had bone abnormalities (see table below).

Table 1 - Patients with histological bone abnormality at baseline and end of treatment

Bone abnormality present	**Alfacalcidol (N=72)**	**Placebo (N=62)**	**p**
At baseline	55 (76.4%)	45 (72.6%)	0.6
End of treatment	39 (45.2%)	51 (82.3%)	0.001

The majority of patients had bone abnormalities at baseline. Therefore, the study does not meet the initial objective to demonstrate prevention of bone abnormalities. Results can only be used to study treatment or progress of bone abnormalities. The results demonstrate a statistically significant difference in patients with bone abnormalities in favour of alfacalcidol. The difference in proportion of patients with bone abnormalities (One-Alpha® - placebo) was -0.28 (95% CI : -0.13 to -0.43). The mean difference of 28% in favour of One-Alpha® is considered clinically relevant, demonstrating efficacy of One-Alpha® in the treatment of bone abnormalities.

Secondary efficacy analysis
Serum parathyroid hormone levels were comparable at baseline which is reflected in the median (Table 2). The high mean PTH level in the alfacalcidol treated group was explained by a small number of patients with high PTH levels. In the placebo-treated group serum PTH levels increased statistically significantly, whereas the alfacalcidol treated group did not show a significant change from baseline. Differences between treatment groups were statistically significant (difference in mean change of -9.33 pmol/l; 95% CI: -14.19, -4.47).

Table 2 - Change in serum PTH and creatinine clearance from baseline to end of treatment

Laboratory parameter		**Alfacalcidol (N=89)**	**Placebo (N=87)**	**p**
PTH (pmol/l)				
At baseline	Mean (sd)	10.31 (15.90)	6.34 (4.57)	0.9
	Median	4.56	5.24	
	Number	79	80	
End of treatment	Mean (sd)	7.77 (9.16)	14.60 (17.63)	0.003
	Median	5.29	8.42	
	Number	84	77	
Change from baseline	Mean	-1.90	7.43	<0.001
	95% CI	-5.44, 1.64	4.05, 10.81	
	Number	76	75	
Difference between groups	Mean	-9.33		
	95%	-14.19, -4.47		
Creatinine clearance (ml/min)				

At baseline	Mean (sd)	31.6 (10.8)	32.9 (11.6)	0.43
	Median	30.0	31.5	
	Number	88	86	
End of treatment	Mean (sd)	26.6 (16.7)	28.7 (17.2)	0.44
	Median	26.0	28.7	
	Number	85	81	
Change from baseline	Mean	-5.0	-4.6	0.85
	95% CI	-8.0, -2.0	-7.7, -1.5	
	Number	85	79	
Difference between groups	Mean	-0.4		
	95%	-4.7, 3.9		

Overall, treatment with alfacalcidol but not placebo reduced serum iPTH levels. This is in line with expectations based on current knowledge of the active compound calcitriol. It is noticed that part of the patients included in the study and receiving alfacalcidol, do not meet current standards for treatment of hyperparathyroidism as reflected in the NKF K/DOQI treatment guidelines. In addition, no information on the percentage of patients reaching treatment targets can be derived from this study because of lack of target ranges for iPTH values by CKD stage for the analysis method used in this study.
Baseline creatinine clearance was comparable for both treatment groups (Table 4). In both treatment groups, creatinine clearance decreased from baseline to end of treatment, but no differences were observed between treatment groups. A decrease of creatinine clearance was anticipated as patients renal function is known to worsen in time. The comparable creatinine clearance indicates that long-term use of alfacalcidol did not have an adverse effect on renal functions.

Serum alkaline phosphatase was analysed using data from the reassay of frozen samples at a central laboratory. Alkaline phosphatase levels were comparable at baseline between treatment groups (154 ± 69 IU/l alfacalcidol treated group versus 152 ± 71 IU/l placebo-treated group). During treatment serum alkaline phosphatase levels were decreased at six months but increased again thereafter in the alfacalcidol treated group. At the end of treatment, serum were still reduced (141 ± 55 IU/l), although not statistically significant, and increased in the placebo-treated group (169 ± 83 IU/l). The difference between treatment groups was statistically significant (difference in mean change -31.4 IU/l; 95% CI: -48.8, -13.9).
During vitamin D deficiency, serum alkaline phosphatase increases which is indicative of worsening bone disease as is observed in the placebo-treated group. Initially, alfacalcidol seems to improve bone disease based on the reduced alkaline phosphatase levels, however, the long-term effect of alfacalcidol on bone turnover remains unknown from the current study.

Serum albumin corrected calcium levels at baseline were comparable between treatment groups (2.36 ± 0.15 mmol/l alfacalcidol treated group versus 2.37 ± 0.14 mmol/l placebo treated group). Corrected calcium levels increased in the alfalcalcidol treated group (mean change: 0.12 mmol/l; 95% CI: 0.07, 0.17 mmol/l) and remained stable in the placebo-treated group (mean change: -0.01 mmol/l; 95% CI: -0.05, 0.03 mmol/l). There was a statistically significant difference in mean change between the groups of 0.13 mmol/l (95% CI: 0.06, 0.19 mmol/l).
Baseline levels of calcium were in the upper range of the target criteria. Hypercalcaemia is a dose-limiting factor for alfacalcidol and dose was titrated based on serum calcium levels. This is adequately stated in the proposed SPC. Occurrence of hypercalcaemia is further discussed in the safety assessment.

Serum sample was insufficient for analysis of $1,25(OH)_2D_3$.
In the vast majority of the patients (≥ 95%) bone pain and myopathy were absent and radiographs of hands were normal at baseline. Also, these parameters did not change upon treatment for ≥ 95% of the patients and no differences were observed between treatment groups.

Conclusion
This study showed that long term treatment with alfacalcidol improved bone abnormalities in stage 3 and 4 CKD patients compared with placebo treatment. Due to the limited number of patients without bone abnormalities, prevention of bone abnormalities could not be demonstrated. However, despite the

absence of data in prevention of renal osteodystrophy, current treatment guidelines state that vitamin D analogs should be considered in patients CKD patients stages 3-5 not on dialysis with elevated iPTH levels and vitamin D deficiency (NKF K/DOQI guidelines 2003, KDIGO 2009). In addition, new clinical trials are not likely to be performed because of the wide-spread use of alfacalcidol in CKD patients. Therefore, based on current clinical practice and the established role of vitamin D in mineral homeostasis, it can be anticipated that alfacalcidol can also play a role in prevention of renal osteodystrophy.
Study OA 186 also showed that treatment with alfacalcidol prevented the increase in serum iPTH levels that was observed in the placebo-treated group, supporting its efficacy in the treatment of secondary hyperparathyroidy in line with current knowledge and common clinical practice. Reference to current treatment guidelines as adequately stated in the SPC prevents the treatment of patients without elevated levels of iPTH as was observed in this study.
The dosing regimen (once daily) and the starting and maintenance dose used in the clinical trials support the proposed posology in the SPC and reflect current common clinical practice.

Study OA 0301 DE

Design

This was a multi-centre, prospective, controlled, parallel group, randomised, open phase III study to evaluate the efficacy of alfacalcidol in the treatment of secondary hyperparathyroidism in patients with chronic renal failure using three different treatment modalities.
Patients (≥ 18 years) with end stage renal disease on haemodialysis three times a week with secondary hyperparathyroidism in patients. Plasma iPTH levels were 15.8 pmol/l < P-iPTH ≤126.4 pmol/l at stratification.
Major exclusion criteria included a serum calcium (total) multiplied by serum phosphate (Ca x P product) > 5.65 $mmol^2/l^2$, use of calcium lowering therapy within two weeks before study entry, concurrent malignancy or clinically significant liver disease at qualification and continuous treatment with anti-epileptics interfering with vitamin D metabolism (short term treatment with anti-epileptics was, however, always allowed).

The study consisted of four phases (see also Table 5). Phase 1 was a qualification phase of two weeks to decide whether the patient was eligible for the study. Eligible patients entered a washout phase of 8 weeks in which treatment with any vitamin D analogue or calcitonin was not allowed as baseline values of calcium, phosphorus and P-iPTH were to be measured at the end of the phase.
Following the washout phase, all patients complying with the inclusion/exclusion criteria were to be stratified (according to P-iPTH levels) and randomised, and proceeded to the treatment phase which lasted 16 weeks. Patients were randomised to treatment with either continuous oral treatment (administration once daily), pulse oral treatment (administration 3 times a week), or pulse i.v. treatment (administration 3 times a week) with alfacalcidol. Phase 4 was a follow-up phase of 4 weeks during which SAEs were recorded. Blood samples were taken before starting the dialysis session.

Patients were treated with the following dosing schedules:
1. Oral once daily alfacalciferol capsules 0.25 µg up to 4 µg/day, to be taken in the morning;
2. Oral three times weekly (intervals of 48 or 72 hours) alfacalciferol capsules 0.25 µg with a maximum of 8 µg/day, administered at the end of each haemodialysis session;
3. I.v. three times weekly (intervals of 48 or 72 hours) alfacalciferol ampoules 2 µg/ml with a maximum of 8 µg/day, administered at the end of each haemodialysis session.

The primary objective was to evaluate the efficacy of alfacalcidol in the treatment of secondary hyperparathyroidism in patients with chronic renal failure using three different treatment modalities.

Secondary objectives were:
1. To compare the efficacy of three different treatment modalities of alfacalcidol in the treatment of secondary hyperparathyroidism in patients with chronic renal failure.
2. To evaluate the safety and tolerability of alfacalcidol in the treatment of secondary hyperparathyroidism in patients with chronic renal failure.

Primary efficacy endpoint
The primary response criterion was the proportion of patients achieving a ≥ 30% reduction in P-iPTH (Nichols Intact assay) from baseline at four consecutive on-treatment visits. Baseline values used for statistical analysis corresponded to values obtained at the end of the washout phase (i.e. at visit 4).

Secondary efficacy endpoint
1. To compare the efficacy of three different treatment modalities of alfacalcidol (p.o. continuous, p.o. pulse and i.v. pulse)
2. In addition to recorded changes in P-iPTH levels (main parameter), the efficacy parameters included:
   - bone formation/resorption parameters: alkaline phosphatase, bAP, Tracp 5b.
   - vitamin D parameters: $1(OH)D_3$ (alfacalcidol), $1,25(OH)_2D_3$ (active vitamin D) and $25OHD_3$ (vitamin D status).

Safety endpoint
The safety endpoints included frequency tabulations of any reported adverse events. For laboratory data, the relationship between the dosing of alfacalcidol and the change in laboratory values was assessed.

Results
A total of 266 patients were enrolled in the study at 22 centres. At the qualification visit 39 patients were disqualified mainly due to a too high Ca x P product. During the washout period 85 patients were withdrawn prior to randomisation, mainly because exclusion criteria emerged during the study. The remaining 142 patients were randomised to study treatment; 49 patients were randomised to p.o. continuous treatment, 45 patients to p.o. pulse treatment and 48 to i.v. pulse treatment. A total of 8 patients did not complete the treatment according to the protocol.

Primary efficacy analysis
The proportion of patients achieving a ≥ 30% reduction in the P-iPTH (Nichols Intact assay) at four consecutive visits in the p.o. continuous treated group was 40/49 (82%), 32/45 (71%) in the p.o. pulse treated group and 35/48 (73%) in the i.v. pulse treated group (Table 3). The p.o. continuous group had a significant higher proportion of treatment success than 60%. The p.o. pulse and i.v. pulse treated groups did not differ significantly from 60%.

Table 3 - The proportion of patients achieving a ≥ 30% reduction in the P-iPTH (Nichols Intact assay) at four consecutive visits (ITT-analysis).

Treatment group	Success/ no. of pt.	Proportion	98.3% CI	p-value*
p.o.continuous	40/49	0.82	(0.65-0.93)	0.0021
p.o.pulse	32/45	0.71	(0.52-0.86)	0.1672
i.v.pulse	35/48	0.73	(0.55-0.87)	0.0883
Total	107/142	0.75	(0.66-0.84)	

* Test for the proportion = 0.60 by exact binomial test within each treatment group

The results from the per protocol analysis set were very similar to the ITT analysis: The proportion of patients achieving a ≥ 30% reduction in the P-iPTH (Nichols Intact assay) at four consecutive visits in the p.o. continuous treated group was 39/47 (83%), 32/43 (74%) in the p.o. pulse treated group and 35/46 (76%) in the i.v. pulse treated group.
Based on the p.o. continuous treatment group, the high proportion (82%) of patients with at least a 30% reduction of iPTH indicates that alfacalcidol is effective in lowering iPTH levels and supporting its well-known use in the treatment of secondary hyperparathyroidism. Despite the absence of any comparator,

given the nature of the disease it is reasonable to assume that this effect cannot be explained by the natural course of the disease. The data support efficacy of the intermittent i.v. dosing regimen which is considered a common dosing regimen in haemodialysis patients
The MAH was requested to calculate the number of patients reaching therapeutic target according to current treatment guidelines. 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.
According to the study protocol, iPTH levels below the lower target level were not a reason for dose adjustment/interruption. However, in accordance with current treatment guidelines monitoring of iPTH and dose adjustment based on the target range of iPTH has been included in the SPC.

Secondary efficacy analyses
The proportion of patients achieving a ≥ 30% reduction in the P-iPTH (Nichols Bio-Intact assay) at four consecutive visits in the p.o. continuous treated group was 42/49 (86%), 31/45 (69%) in the p.o. pulse treated group and 34/48 (71%) in the i.v. pulse treated group. These results were comparable with the primary efficacy analysis based on the Nichols Intact assay.
Statistical analyses did not reveal differences in primary efficacy criterion between treatment groups.
For all laboratory parameters box-and-whisker plots were examined. P-iPTH tended to increase during the washout period and to decrease again during treatment, but inter-patient variability was large.

In addition, for all laboratory parameters the mean was plotted along with the mean dose of alfacalcidol. For S-phosphate, B-Ca (ionised), S-Ca (total) $1,25(OH)_2D_3$ these parameters seemed to increase in parallel with the increases in alfacalcidol dose.
During the 16-week treatment, there was a statistically significant decrease in serum alkaline phosphatase levels with mean values of 105-113 U/l at baseline vs. 84-101 U/l at the last visit (Mean ± sd: p.o. continuous group: 104.5 ± 51.4 U/l at baseline and 83.9 ± 27.9 U/l at week 16; p.o. pulse group: 112.4 ± 49.4 U/l at baseline and 100.9 ± 49.5 U/l at week 16; i.v. pulse group: 113.0 ± 51.6 U/l at baseline and 100.1 ± 48.4 U/l at week 16).

There was no evidence that the proportion of patients achieving a ≥ 30% reduction in the P-iPTH varies across treatment and study centre, sex, age group and disease severity of secondary hyperparathyroidism. The youngest age group (30-49 years) tended to have a lower overall proportion of treatment success, although it should be noted that the proportion is only based on 20 patients.

Conclusion
In this study, performed in stage 5 CKD patients on haemodialysis, alfacalcidol orally once daily reduced iPTH levels in the majority of the patients. The high proportion (82%) 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. Despite the absence of any comparator, given the nature of the disease it is reasonable to assume that this effect can not be explained by the natural course of the disease. In a post-hoc subanalysis 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. Again, reference to current treatment guidelines as adequately stated in the SPC prevents the treatment of patients without elevated levels of iPTH. iPTH levels below the lower target level were not a reason for dose adjustment/interruption. However, in accordance with current treatment guidelines monitoring of iPTH and dose adjustment based on the target range of iPTH has been included in the SPC to reduce the risk of adynamic bone disease. The once daily oral dosing regimen is in line with that proposed in the SPC and reflects current common clinical practice. The three weekly oral dosing regimen was considered not proven during the national procedure because of limitations in study design and withdrawn from the SPC by the MAH before the MRP started.
Data from study OA 0301 DE also support efficacy of the intermittent i.v. dosing regimen in the treatment of secondary hyperparathyroidism which is considered an established dosing regimen in haemodialysis patients.

Additional data

The conclusions of the pivotal studies are further supported by data from two open uncontrolled studies OA 187 and UA 190 F, showing that intermittent i.v. dosing of alfacalcidol was effective in lowering iPTH levels in patients on haemodialysis. In addition, the observed lowering of alkaline phophatase suggests improvement of bone disease. Despite the absence of data on bone histology, based on current knowledge it is reasonable to assume that also intermittent i.v. dosing of alfacalcidol in haemodialysis patients plays a role in prevention and treatment of renal osteodystrophy, depending on the mineral status of the patient. The dosing regimen is in line with current standard clinical practice.

For all treatment formulations, it is adequately stated in the SPC that alfacalcidol should be used in the context of a multiple therapeutic approach and that regular monitoring of calcium, phosphate, iPTH and calcium x phosphorus levels is required.

The efficacy of alfalcalcidol in children is acknowledged based on its widespread use in clinical daily practice. The oral dose of 10-20 ng/kg/day is considered to be adequately supported by literature references including some recently performed studies.

Clinical Safety

Overall, the reported adverse events (AEs) were of mild to moderate intensity in both studies and the number of AEs related to alfacalcidol treatment was limited. Most AEs relate to the secondary effects of alacalcidol on phosphate and especially calcium absorption (increased absorption). The most common short term adverse events associated with alfacalcidol treatment relate to hypercalcaemia. The clinical features of hypercalcaemia include anorexia, constipation, nausea, vomiting, headache, weakness, apathy and somnolence. More severe manifestations may include fever, thirst/polydipsia, dehydration, polyuria, nocturia, abdominal pain, paralytic ileus, cardiac arrhythmias and psychiatric disturbances. Rarely, overt psychosis and metastatic calcification (particularly nephrocalcinosis and renal stones) may occur. The clinical studies showed that treatment related AEs can be limited by titrating alfacalcidol dose based on serum calcium levels. In addition, alfacalcidol increases gastrointestinal absorption of phosphate which may aggravate hyperphosphataemia. Again, the occurrence of hyperphosphataemia was limited as patients were treated for high phosphate levels and alfacalcidol dosage also is adjusted based on phosphate levels. Another potential safety concern with alfacalcidol is occurrence of low bone turnover disease or adynamic bone disease because of oversuppression of PTH levels. There were no reports of adynamic bone disease, whereas efficacy data showed that some patients had very low iPTH levels. A study by Hamdy (1995) showed that treatment with alfacalcidol can result in adynamic bone disease in patients with mild to moderate renal failure. It is likely that this over-suppression of iPTH is manageable with adherence to current treatment guidelines in which dose adjustments are based on monitoring of iPTH with specified targets for each CKD stage. This is adequately reflected in the SPC. Overall, alfacalcidol treatment is part of a multitherapeutic approach including treatment of hypocalcaemia and hyperphosphataemia and dose adjustments are made upon regular monitoring of calcium, phosphate, PTH and calcium x phosphate product thereby limiting the incidence of adverse events.

Information on long term treatment with alfacalcidol in clinical trials is limited. The main concern with vitamin D metabolites is the risk of inducing or accelerating the progression of renal failure. The current long term study over two years (OA 186) did not indicate a more rapid decline in renal function compared with placebo at the currently used dosages. The limited data from clinical trials can be acceptable when combined with data from post-marketing surveillance, as alfalcalcidol is available on the market for about thirty years. Again, most reported AEs relate to hypercalcaemia. No new safety signals were identified and these data are considered to support the safety profile of alfacalcidol in the proposed indications in both adults and children.

Pharmacovigilance plan/risk management plan

The Pharmacovigilance system described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MAH committed to file a variation for the update of the Pharmacovigilance System.

An updated version of the European Risk management plan has been provided and is acceptable.

Product information

SPC

In 2008 the MAH filed a variation to update information on amongst others the quality and clinical part of the dossier. The main change in the SPC involved a rewording of the indication in line with current treatment insights and current clinical practice (NKF K/DOQI treatment guidelines 2003) and an extension in posology for the treatment of secondary hyperparathyroidism in stage 5 chronic kidney disease (CKD) patients (pulse treatment in addition to continuous treatment). During the variation procedure, the extension in posology was not approved because of lack of well-designed clinical trials.

Readability test

The package leaflet has not been evaluated via a user consultation study, as a bridging report was provided. Reference was made to a successful user test on the PIL for One-Alpha 2 micrograms/ml oral drops, solution. Content, visual presentation and key safety messages for both PILs were analyzed, based on which a waiver could be granted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB, on the basis of the data submitted, considered that Etalpha LEO 0.25, 0.5 and 1 microgram, capsules, soft demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. The date of authorisation in the Netherlands was 4 August 1978 for the 1 µg capsules, 8 January 1980 for 0.25 µg and 30 August 1999 for the 0.5 µg product. The other member states mutually recognised the Dutch evaluation for the marketing authorisation.

The chemical-pharmaceutical quality of the drug substance and finished product has been sufficiently demonstrated.

For this application, the MAH submitted a total of 7 clinical studies: three pharmacokinetic studies, four studies in patients with renal failure. Clinical efficacy and safety have been demonstrated in support of the approved indications.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and were adequately updated in accordance with current treatment insights and clinical practice.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 14 April 2010.

A European harmonised birth date has been allocated (28 February) and subsequently the first data lock point for alfacalcidol is 28 February 2012. The first PSUR will cover the period from 1 March 2010 to 28 February 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 13 May 2015.

The following post-approval commitment has been made during the procedure:

Pharmacovigilance

- The MAH committed to file a variation for an update of the Pharmacovigilance System.

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CKD	Chronic Kidney Disease
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
iPTH	Intact Parathyroid Hormone
ITT	Intention to Treat
i.v.	intravenous
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
PTH	Parathyroid Hormone
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached