Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

One-Alpha 0.25 microgram soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.25 micrograms of Alfacalcidol.

Excipient(s) with known effect: Sesame oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft (capsule).

Cream-coloured, egg-shaped soft gelatin capsule holding 0.1g oily solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

One-Alpha is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1 α-hydroxylation of vitamin D3 such as when there is reduced renal function.

The main indications are:

a) Uraemic bone disease.
b) Hyperparathyroidism (with bone disease).
c) Hypoparathyroidism.
d) Post-menopausal, senile and steroid-induced osteoporosis.
e) Nutritional and malabsorptive rickets and osteomalacia.
f) Pseudo-deficiency (D-dependent) rickets.
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia.
h) Prophylactic and therapeutic use in neonatal hypocalcaemia.

4.2 Posology and method of administration

Posology:

For most conditions, One-Alpha is given as a daily dose, with the exception of those patients undergoing haemo- or peritoneal dialysis, when doses may be given as pulsed therapy on 2 or 3 days per week.

Once daily treatment:
Initial dosage for all indications is:

- Adults and children over 20 kg bodyweight 1 microgram/day
- Neonates and premature infants 0.05-0.1 microgram/kg/day
- Children under 20 kg bodyweight 0.05 microgram/kg/day
- Elderly 0.5 microgram/day may be sufficient

Regular monitoring of response by assays of serum calcium and phosphate, parathyroid hormone and alkaline phosphatase levels and urinary calcium may be used as a guide for subsequent dosage.

Most patients respond eventually to doses between 0.5 - 6 micrograms daily. The dosage requirements generally decrease in bone disorders at a time when there is biochemical or radiographic evidence of bone healing, and in hypoparathyroid patients after normal plasma calcium levels have been attained. Maintenance doses are generally in the range of 0.25 - 2 micrograms daily.

Two-three times weekly treatment:

This is an alternative dosing schedule only for the intermittent treatment of uraemic bone disease in adult patients requiring dialysis.

For this indication only, intermittent treatment with One-Alpha capsules following each haemodialysis/peritoneal dialysis session may also be used. In this situation, the prescriber must be suitably qualified and experienced in the management of uraemic bone disease.

The initial dosage is 0.5 - 2 micrograms 2 - 3 times a week. The dose of One-Alphamust be carefully determined for each patient by monitoring serum levels of parathyroid hormone (PTH), calcium and phosphate and the dose adjusted by increments of 0.25 - 0.5 micrograms until clinical target ranges of these parameters are achieved.

For patients already receiving regular haemodialysis or peritoneal dialysis and on daily oral One-Alpha treatment, on transition to this intermittent dosing schedule each individual initial intermittent dose is calculated as: current daily dose ×7/3 (if dose is three times weekly, or x7/2 if two times weekly). The resulting dosage can be rounded to multiples of 0.25 micrograms and administered 3 or 2 times per week respectively at the end of each dialysis session. The initial total weekly dose should be the same regardless of the dosage regime chosen (daily or intermittent).

a) Uraemic bone disease

Most patients with osteitis fibrosa and osteomalacia show a rapid symptomatic and a gradual biochemical, radiographic and histological improvement. In these patients, the only unwanted effects of One-Alpha appears to be hypercalcaemia which is more likely when there is evidence of bone healing. Patients with relatively high initial calcium levels may have autonomous hyperparathyroidism which is often unresponsive to One-Alpha. In these cases other therapeutic measures may be indicated.

Before and during treatment with One-Alpha, phosphate-binding agents should be considered to prevent hyperphosphataemia, which is known to increase the risk of metastatic calcification, especially when associated with hypercalcaemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

Early hypercalcaemia is more likely in patients with autonomous hyperparathyroidism, those with histologically 'pure' osteomalacia related possibly to phosphate depletion or aluminium intoxication, and those dialysed against a high dialysate calcium concentration.

b) Hyperparathyroidism (with bone disease)

Following parathyroidectomy, patients with primary or tertiary hyperparathyroidism and bone disease often require large doses of vitamin D and intravenous calcium to avoid severe hypocalcaemia. Preliminary studies suggest that pre-operative treatment with One-Alpha for 2 to 3 weeks alleviates bone pain and myopathy when present without aggravating pre-operative hypercalcaemia. Continued post-operative treatment decreases post-operative hypocalcaemia and should be continued until the plasma alkaline phosphatase level falls to normal or hypercalcaemia occurs.

c) Hypoparathyroidism

In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with One-Alpha. Severe hypocalcaemia (e.g. after extensive neck surgery) is corrected and symptoms abolished even more rapidly with higher doses of One-Alpha (e.g. 3-5 micrograms) together with calcium supplements. Normocalcaemia may be maintained with smaller doses within a relatively narrow dose range.

d) Post-menopausal, senile and steroid-induced osteoporosis

Patients with post-menopausal and senile osteoporosis are said to have low levels of plasma 1,25-$(OH)_2D_3$, even though their nutritional vitamin D status is normal. This may explain why some of these patients have calcium malabsorption, which is relatively resistant to vitamin D but responsive to small doses of One-Alpha. Many post-menopausal osteoporotic women appear to have both oestrogen deficiency and calcium malabsorption. To avoid hypercalcaemia, a daily dose of 1 microgram of One-Alpha should not be exceeded and excessive calcium supplementation is not indicated.

e) Nutritional and malabsorptive rickets and osteomalacia

Nutritional rickets and osteomalacia can be cured rapidly with 'physiological' doses of One-Alpha. Limited experience suggests that patients with malabsorptive osteomalacia (responding only to large doses of parenterally administered vitamin D) will respond to small doses of One-Alpha.

f) Pseudo-deficiency (D-dependent) rickets

Although large doses of parent vitamin D would be required (probably because of an inherent defect in the production of 1,25-$(OH)_2D_3$), effective doses of One-Alpha are similar to those required to heal nutritional vitamin D deficiency rickets.

g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia

These conditions are characterised by hypophosphataemia due to defective tubular reabsorption and intestinal absorption of phosphorous. Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory, the latter tending to produce hypocalcaemia and hyperparathyroidism. Treatment of children and adults with One-Alpha rapidly relieves myopathy when present, increases calcium and phosphorous retention and promotes bone healing. Phosphate supplements may also be required in some patients.

h) Prophylactic and therapeutic use in neonatal hypocalcaemia

Although the normal starting dose of One-Alpha is 0.05-0.1 micrograms/kg/day (and subsequent adjustment is by careful titration), in severe cases doses of up to 2 micrograms/kg/day may be required. Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase may be markedly raised in the pre-term low birthweight infant. Whilst levels of 5 times the normal adult

laboratory value may be usual in this group, alkaline phosphatase levels above 7.5 times the adult range indicate active disease. A dose of 0.1 micrograms/kg/day has proved effective as prophylaxis against early neonatal hypocalcaemia in premature neonates.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypercalcaemia.

4.4 Special warnings and precautions for use

During treatment with One-Alpha, serum calcium and serum phosphate levels should be monitored regularly. PTH, alkaline phosphatase and the calcium x phosphate product should be monitored as clinically indicated.

Hypercalcaemia might appear in patients treated with One-Alpha. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. Signs of hypercalcaemia are anorexia, fatigue, nausea and vomiting, constipation or diarrhoea, polyuria, sweating, headache, polydipsia, hypertension, somnolence and vertigo.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). One-Alpha may then be restarted at a reduced dose (half the previous dose) with monitoring of calcium.

Prolonged hypercalcaemia may aggravate arteriosclerosis, cardiac valve sclerosis or nephrolithiasis and therefore prolonged hypercalcaemia should be avoided when One-Alpha is used in these patients. Transient or even long-lasting deterioration of kidney function has been observed. One-Alpha should also be used with caution in patients with calcification of pulmonary tissue as this may result in cardiac disease.

In patients with renal bone disease or severely reduced renal function, a phosphate binding agent could be used simultaneously with alfacalcidol to prevent increased serum phosphate and potential metastatic calcification.

One-Alpha should be used with caution in patients with granulomatous diseases such as sarcoidosis where the sensitivity to vitamin D is increased due to increased hydroxylation activity.

Concurrent use of digitalis glycosides in the presence of hypercalcaemia due to vitamin D administration increases the potential for cardiac arrhythmias.

Use with caution in patients being treated with thiazide diuretics as they may have an increased risk of developing hypercalcaemia.

One-Alpha capsules contain sesame oil as an excipient. Sesame oil may rarely cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interactions

<u>Thiazide diuretics and calcium-containing preparations</u>
Concurrent use of thiazide diuretics or calcium-containing preparations may enhance the risk of hypercalcaemia. Calcium levels should be monitored.

<u>Vitamin D containing preparations/Other Vitamin D analogues</u>
Concurrent use of vitamin D containing preparations with alfacalcidol may enhance the risk of hypercalcaemia. Use of multiple vitamin D analogues should also be avoided.

<u>Anticonvulsants</u>
Anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine or primidone) have enzyme- inducing effects resulting in an increased metabolism of alfacalcidol. Patients taking anticonvulsants may require larger doses of One-Alpha.

<u>Magnesium containing antacids</u>
Absorption of magnesium-containing antacids may be enhanced by One-Alpha, increasing the risk of hypermagnesaemia.

<u>Aluminium-containing preparations</u>

One-Alpha may increase the serum concentration of aluminium. Patients taking aluminium containing preparations (e.g. aluminium hydroxide, sucralfate) should be monitored for signs of aluminium related toxicities.

Bile acid sequestrants
Concomitant oral administration of bile acid sequestrants such as cholestyramine may impair the intestinal absorption of oral One-Alpha formulations. One-Alpha should be administered at least 1 hour before, or 4 to 6 hours after the intake of the bile acid sequestrant in order to minimize the potential risk of interaction.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

One-Alpha should not be used in pregnancy unless clearly necessary as hypercalcaemia during pregnancy may produce congenital disorder in the offspring. Caution should be exercised in women of childbearing potential.

Breast-feeding
Alfacalcidol is excreted in human milk. A decision must be made whether to discontinue breast- feeding or to discontinue/abstain from One-Alpha therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Breast-fed infants of alfacalcidol-using mothers should be monitored closely for hypercalcaemia.

Fertility
There are no clinical studies on the effect of One-Alpha on fertility. A pre-clinical study did not show an effect on fertility in rats.

4.7 Effects on ability to drive and use machines

Alfacalcidol has no or negligible direct influence on the ability to drive and use machines. However, the patient should be informed that dizziness may occur during treatment and take this into account while driving or using machines.

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and spontaneous reporting.

The most frequently reported undesirable effects are various skin reactions such as pruritus and rash, hypercalcaemia, gastrointestinal pain/discomfort and hyperphosphataemia.

Renal failure has been reported post-marketing.

Undesirable effects are listed by MedDRA system organ class (SOC) and the individual undesirable effects are listed starting with the most frequently reported one. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common ≥1/10
Common ≥1/100 to < 1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000

Metabolism and nutrition disorders	
Common:	Hypercalcaemia Hyperphosphatemia
Psychiatric disorders	
Uncommon:	Confusional state

Nervous system disorders	
Uncommon:	Headache
Rare:	Dizziness
Gastrointestinal disorders	
Common:	Abdominal pain and discomfort
Uncommon:	Diarrhoea Vomiting Constipation Nausea
Skin and subcutaneous tissue disorders	
Common:	Rash* Pruritus *Various types of rash reactions such as erythematous, maculo-papular and pustular have been reported
Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia
Renal and urinary disorders	
Common:	Hypercalciuria
Uncommon:	Renal impairment (including acute renal failure) Nephrolithiasis/ Nephrocalcinosis
General disorders and administration site conditions	
Uncommon:	Fatigue/asthenia/malaise Calcinosis

Paediatric population
The observed safety profile is similar for children and adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Excessive intake of One-Alpha may lead to the development of hypercalcaemia, however, the effect is reversed rapidly on withdrawal.

In severe cases of hypercalcaemia general supportive measures should be undertaken: keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal functions indices, assess electrocardiographic abnormalities, especially on patients on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium contents should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: A11C C03
Alfacalcidol is converted rapidly in the liver to 1,25 dihydroxyvitamin D_3. This is the metabolite of vitamin D_3 which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of One-Alpha and 1,25 dihydroxyvitamin D_3 are very similar.

Impaired renal 1-α-hydroxylation reduces 1,25 dihydroxyvitamin D_3 production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and vitamin D dependent rickets. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of One-Alpha.

The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse.

The major advantage of One-Alpha is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

Serum levels of 1,25 dihydroxyvitamin D_3 reach peak concentrations approximately 8-12 hours after a single dose of One-Alpha with a half-life of 1,25-(OH)2 -D3 of about 35 hours.

The metabolism is similar to that of vitamin D after the 25-hydroxylation to 1,25 dihydroxyvitamin D_3.

5.3 Preclinical safety data

The non-clinical 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.

Alfacalcidol is not genotoxic.

No specific effects of alfacalcidol on fertility or behaviour of the offspring were noted in rats and rabbits. In terms of embryo-foetal development, foetal toxicity (post-implantation loss, lower litter size and lower pup weight) was observed at doses high enough to cause toxicity in the dams. High doses of vitamin D are known to be teratogenic in experimental animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sesame Oil, refined
All-rac-α-tocopherol

Capsule Shell
Gelatin
Glycerol (E422)
Potassium sorbate (E202)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al/PVC blister foil, polyamide/Al lid containing 30 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/017/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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