Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

One-Alpha 2 micrograms/ml oral drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol 2 micrograms/ml. Each drop (0.05 millilitre) contains 0.1 micrograms (100 nanograms) alfacalcidol.

Excipients with known effect:
Ethanol equivalent to 14 vol%, methylparahydroxybenzoate (E218) 1.5 mg/ml, macrogolglycerol hydroxystearate 22.6 mg/ml, sorbitol (E420) 452 mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral drops, solution.

Slightly turbid to clear, colourless 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 a-hydroxylation such as when there is reduced renal function.

The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Neonatal hypocalcaemia
e) Nutritional and malabsorptive rickets and osteomalacia
f) Pseudo-deficiency (D-dependent) rickets and osteomalacia
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia.

4.2 Posology and method of administration

Posology

Initial dose for all indications:

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

To administer this medicine hold the dropper in a vertical position, upside down. The drops should flow immediately but if they do not, tap the bottle gently. Do not shake the bottle.

Half-drop doses should be rounded up to the next whole number of drops.

Plasma levels should initially be measured at weekly intervals. The daily dose of One-Alpha may be increased by increments of 0.25-0.5 microgram. When the dose is stabilised, measurements may be taken every 2-4 weeks.

Most adult patients respond to doses between 1 and 3 micrograms per day. When there is biochemical or radiographic evidence of bone healing (and in hypoparathyroid patients when normal plasma calcium levels have been attained), the dose generally decreases. Maintenance doses are generally in the range of 0.25 to 1 microgram per day. If hypercalcaemia occurs, One- Alpha should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

a) Renal bone disease:

Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to One-Alpha. Other therapeutic measures may be indicated.

Before and during treatment with One-Alpha, phosphate-binding agents should be considered to prevent hyperphosphataemia. 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.

b) Hyperparathyroidism:

In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, pre-operative treatment with One-Alpha for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia, One-Alpha should be continued until plasma alkaline phosphatase levels fall 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 is corrected more rapidly with higher doses of One-Alpha (e.g. 3-5 micrograms) together with calcium supplements.

d) Neonatal hypocalcaemia:
Although the normal starting dose of One-Alpha is 0.05-0.1 microgram/kg/day (followed by careful titration) in severe cases doses of up to 2 microgram/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 approximately 7.5 times above the adult range indicates active disease.
A dose of 0.1 microgram/kg/day of One-Alpha has proven effective as prophylaxis against early neonatal hypocalcaemia in premature infants.

e) Nutritional and malabsorptive rickets and osteomalacia:

Nutritional rickets and osteomalacia can be cured rapidly with One-Alpha. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of One-Alpha.

f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:

Although large doses of parent vitamin D would be required, effective doses of One-Alpha are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:

Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with One-Alpha at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

Method of administration

One-Alpha Drops should be administered orally, using the integral dropper. One drop = 0.1 microgram.

4.3 Contraindications

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

Hypercalcaemia, metastatic calcification.

4.4 Special warnings and precautions for use

During treatment with One-Alpha, serum calcium and serum phosphate levels should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses. PTH, alkaline phosphatase and calcium phosphates 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 muscle and bone pain, muscle weakness, confusion, dehydration, anorexia, fatigue, nausea and vomiting, constipation, polyuria, sweating, headache, polydipsia, hypertension and somnolence.

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-Alphashould 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-Alphashould 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.

One-Alpha oral drops contain up to 340 mg ethanol per dose (corresponding to 6 micrograms of alfacalcidol), which is equivalent to 14 vol%. The amount of ethanol in each dose of One-Alpha is equivalent to less than 9 ml beer or 4.5 ml wine. The small amount of ethanol in One-Alpha will not have any noticeable effect. The alcohol content may need be taken into account for young children.

One-Alpha oral drops contain 452 mg sorbitol in each ml. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

One-Alpha oral drops contain methylparahydroxybenzoate as an excipient. Methylparahydroxybenzoate may cause allergic reactions (possibly delayed).

One-Alpha oral drops contain macrogolglycerol hydroxystearate as an excipient. Macrogolglycerol hydroxystearate may cause stomach upset and diarrhoea.
One-Alpha oral drops contain less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

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.

Other vitamin D containing preparations
Concurrent use of other vitamin D containing preparations may enhance the risk of hypercalcaemia. Use of multiple vitamin D analogues should be avoided.

Anticonvulsants
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.

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

Aluminium-containing preparations
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 minimise 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
Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders	
Common:	Hypercalcaemia Hyperphosphataemia
Psychiatric disorders	
Not known:	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 such as erythematous, maculo-papular and pustular have been reported
Not known:	Urticaria
Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia
Renal and urinary disorders	
Common:	Hypercalciuria
Uncommon:	Nephrolithiasis/ Nephrocalcinosis
Not known:	Renal impairment (including acute renal failure)
General disorders and administration site conditions	
Uncommon:	Fatigue/asthenia/malaise Calcinosis

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 function indices, assess electrocardiographic abnormalities, especially in patients on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content 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-$(OH)_2$-D_3 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

Ethanol
Macrogolglycerol hydroxystearate
Methylparahydroxybenzoate (E218)
Citric acid monohydrate (E330)
Sodium citrate (E331)
Sorbitol (E420)
All-rac-α-tocopherol

Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening: the shelf-life is 4 months when stored at 2 to 8°C (in a refrigerator).

6.4 Special precautions for storage

Store at 2 to 8°C (in a refrigerator). Keep the container in the outer carton.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottles of 10 and 20 ml, fitted with a polyethylene dropping device and a polypropylene screw cap.

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

PA2239/017/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 2nd March 2008

10 DATE OF REVISION OF THE TEXT

May 2021