One-Alpha®

1. NAME OF MEDICINAL PRODUCT

One-Alpha®
Alfacalcidol

Carefully read this insert before administering this product. It contains information about your treatment. If you have any doubt or you are not sure about something, please ask your physician or Pharmacist chemist. Keep this insert as you might need to read it again.
Verify this product fully corresponds to the one prescribed by your physician.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules
Alfacalcidol 0.25 microgram, 0.5 microgram and 1 microgram
Pack sizes: 10, 30, 50 and 100 capsules
Excipients the clinician should be aware of: Sesame oil

Drops
Alfacalcidol 2 micrograms/ml (one drop provides 0.1 microgram)
Excipients the clinician should be aware of: Ethanol, sorbitol, methyl parahydroxybenzoate, macrogolglycerol hydroxystearate
Pack sizes: 10 ml and 20 ml

Solution for injection
Alfacalcidol 2 micrograms/ml (for i.v. use)
Pack sizes: 0.5 ml x 10 ampules and 1 ml x 10 ampules
List of excipients, see section 6.1

Not all pack sizes, strengths and formulations may be marketed

3. PHARMACEUTICAL FORM

Capsules
Soft capsules; cream-coloured (0.25 microgram), pink (0.5 microgram), or brownish (1 microgram)

Drops
Oral drops; slightly cloudy to clear, colourless

Solution for injection
Solution for injection (for i.v. use); clear and colourless

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diseases caused by disturbances in the calcium metabolism in consequence of reduced endogenous production of 1.25-dihydroxyvitamin D_3. Renal osteodystrophy, postoperative or idiopathic hypo-parathyroidism, pseudohypoparathyroidism, as an adjunct to the management of tertiary hyperparathyroidism, vitamin D-resistant rickets or osteomalacia, vitamin D-dependent rickets, neonatal hypocalcaemia or rickets, malabsorption of calcium, osteoporosis, malabsorptive and nutritional rickets, and osteomalacia.

4.2 Posology and method of administration

Individual dosage under thorough control of serum calcium.
Adults and children over 20 kg: Initially 1 microgram daily
Maintenance dose: Usually 0.25 – 2 micrograms daily
Children (>1 month) under 20 kg: Initially 0.05 microgram/kg/day
One-Alpha® drops to neonates (<1 month): 0.1 micrograms/kg/day
One-Alpha® drops must be taken orally.
One-Alpha® capsules must be swallowed whole.

One-Alpha® solution for injection is intended for intravenous injection and should be injected slowly. Must be shaken before use.
Elderly: There is no specific clinical experience in the treatment of elderly patients. Special attention is not deemed necessary. Reduced renal function: See section 4.4.
Reduced liver function: With severe liver insufficiency the hydroxylation of 1α-hydroxy vitamin D_3 to 1.25 dihydroxy vitamin D_3 may be reduced, and the intestinal absorption may be reduced because of decreased enterohepatic circulation. A higher dosage may be necessary.
One-Alpha® can be given as an i.v. injection following each haemodialysis. The injection should be administered into the return line from the haemodialysis machine at the end of each dialysis. The initial dosage for adults is 1 microgram per dialysis. The maximum dose recommended is 6 micrograms per dialysis and not more than 12 micrograms per week.
Food intake: It is not known whether the effect of One-Alpha® is affected if taken together with food.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
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.

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

One-Alpha® oral drops contain 14 vol % ethanol (alcohol) as an excipient, i.e. up to 340 mg ethanol per dose (corresponding to 6 micrograms of alfacalcidol). The alcohol content may be harmful to those suffering from alcoholism. The alcohol content must be taken into account in pregnant or breastfeeding women, children and high- risk groups such as patients with liver disease or epilepsy.

Because of the ethanol content, One-Alpha® oral drops should not be used together with disulfiram or products with a disulfiram-type effect.

One-Alpha® oral drops contain sorbitol as an excipient and 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® solution for injection contains 10 vol % ethanol (alcohol) as an excipient, i.e. up to 160 mg ethanol per dose (corresponding to 4 micrograms of alfacalcidol). The alcohol content may be harmful to those suffering from alcoholism. The alcohol content must be taken into account in pregnant or breastfeeding women, children and high- risk groups such as patients with liver disease or epilepsy.

One-Alpha® solution for injection contains 0.14 mmol sodium per dose (corresponding to 4 micrograms of alfacalcidol). Products containing less than 1 mmol sodium (23 mg) per dose are considered essentially 'sodium-free'.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Thiazide diuretics and calcium containing preparations

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.

For One-Alpha® oral formulations only:

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 are limited amount of data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity.

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 breastfeeding 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.

Breastfed 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 THE 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 such as erythematous, maculopapular 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.

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 IV infusion of saline (force diuresis), measure electrolytes, calcium, and renal functions indices, assess electrocardiographic abnormalities, especially on patients using digitalis.
More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium contents should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification

A11CC03 – Vitamin D and analogues

5.1 Pharmacodynamic properties

Alfacalcidol is a potent vitamin D_3 analogue. It converted rapidly and virtually completely in the liver to calcitriol, which is the active metabolite of vitamin D_3. Alfacalcidol stimulates gastrointestinal absorption of calcium and phosphate, and tubular reabsorption of calcium. Via suppression of the parathyroid hormone, reduces phosphate excretion in the urine. Calcitriol is important for demineralisation and remineralisation of bone tissue.

5.2 Pharmacokinetic properties

Absorption: Rapid and almost complete
Half-life: Calcitriol approx. 35 hours. The biological effect remains approx. 3-5 days after discontinuation.
Excretion: Mainly through faeces, some also through urine.

5.3 Preclinical safety data

The pre-clinical toxicity of alfacalcidol is assigned to the known vitamin D effect of calcitriol on calcium homeostasis, which is characterized by hypercalcemia, hypercalciuria and eventually soft tissue calcification. Alfacalcidol is not genotoxic. Effects of alfacalcidol on fertility or behavior in the offspring of rats and rabbits have not been observed. With regard to fetal development, fetal toxicity (post-implantation loss, reduced litter size and reduced birth weight) were observed at doses high enough to cause toxicity in maternal animals. High doses of vitamin D are known to be teratogenic in animals.

6. PHARMACEUTICAL DATA

6.1 Excipients

Capsules

0.25 microgram capsules: Sesame oil; all-rac-α-tocopherol; gelatine (bovine); glycerol; potassium sorbate (E202); titanium dioxide (E171).
0.5 microgram capsules: Sesame oil; all-rac-α-tocopherol; gelatine (bovine); glycerol; potassium sorbate (E202); titanium dioxide (E171); red iron oxide (E172).
1 microgram capsules: Sesame oil; all-rac-α-tocopherol; gelatine (bovine); glycerol; potassium sorbate (E202); red iron oxide (E172); black iron oxide (E172).

Drops

Citric acid monohydrate; ethanol, anhydrous; macrogolglycerol hydroxystearate; methyl parahydroxy benzoate (E218); sodium citrate; sorbitol (E420); α-tocopherol; purified water.

Solution for injection

Citric acid monohydrate; ethanol, anhydrous; sodium citrate; propylenglycol; water for injection.

6.2 Incompatibilities

Not relevant

6.3 Shelf life
Capsules: 3 years
Drops: 3 years
Solution for injection: 3 years

6.4 Special precautions for storage
Capsules
Protect from direct sunlight; store below 25 °C.

Drops
Keep bottle in outer carton to protect from direct sunlight; store at 2-8 °C.

Solution for injection
Keep ampoules in outer carton to protect from light; store at 2-8 °C.

6.5 Nature and contents of container
Capsules
Blister (aluminium/PVC blister with a surface of polyamide/aluminium).

Drops
Brown bottles with dropper (glass bottle type III) with a screw cap of polypropylene and a dropper insert of polyethylene.

Solution for injection
Amber glass ampoule (glass ampoules type I).

6.6 Instructions for handling and disposal
No special instructions.

7. MANUFACTURER
Solution for injection
CENEXI, 52, rue Marcel et Jacques Gaucher, 94120 Fontenay-sous Bois, France for CHEPLAPHARM Arzneimittel GmbH, Ziegelhof 24, 17489 Greifswald, Germany

Capsules and Drops
LEO Pharma A/S, 55, Industriparken, DK-2750 Ballerup, Denmark for CHEPLAPHARM Arzneimittel GmbH, Ziegelhof 24, 17489 Greifswald, Germany

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