

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 0.5 microgram Capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol 0.5 microgram capsule, soft: Each capsule contains 0.5 microgram of alfacalcidol

Excipient with known effect

Each soft capsule contains 98.7 mg arachis oil (peanut oil).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Alfacalcidol 0.5 mcg Capsule, soft (capsule): Light pink coloured, oval shaped soft gelatin capsules containing clear oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The main indications are:

- a) Renal osteodystrophy
- b) Hyperparathyroidism (with bone disease)
- c) Hypoparathyroidism
- d) 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

The dose of Alfacalcidol should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response. Indices of response include plasma levels of calcium (ideally corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Plasma levels should initially be measured at weekly intervals. The daily dose of Alfacalcidol may be increased by increments of 0.25-0.5 microgram. When the dose is established, plasma levels of calcium, phosphorous and creatinine should 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, Alfacalcidol 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 Alfacalcidol. Other therapeutic measures may be indicated.

Before and during treatment with Alfacalcidol, 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 Alfacalcidol for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia, Alfacalcidol 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 Alfacalcidol. Severe hypocalcaemia is corrected more rapidly with higher doses of Alfacalcidol (e.g., 3-5 micrograms) together with calcium supplements.

d) Neonatal hypocalcaemia:

Although the normal starting dose of Alfacalcidol 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 Alfacalcidol 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 Alfacalcidol. Malabsorptive

osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of Alfacalcidol.

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

Although large doses of parent vitamin D would be required, effective doses of Alfacalcidol 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 Alfacalcidol 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

For oral administration

4.3 Contraindications

Hypersensitivity to the active substance, arachis oil (peanut oil), soya or to any of the excipients listed in section 6.1.

Hypercalcaemia, metastatic calcification.

4.4 Special warnings and precautions for use

Monitoring

During treatment with Alfacalcidol, 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

Hypercalcaemia may appear in patients treated with Alfacalcidol. 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.

In case of hypercalcaemia, Alfacalcidol treatment should be stopped until serum calcium concentrations return to normal, usually in about 1 week. Alfacalcidol may then be restarted at half the last dose used with monitoring of calcium.

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

Renal

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.

Granulomatous diseases

Alfacalcidol 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.

Fructose intolerance and peanut allergy

Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Alfacalcidol soft capsules contain arachis oil (peanut oil) and must not be taken by patients known to be allergic to peanut or soya.

4.5 Interaction with other medicinal products and other forms of interaction

Digitalis glycosides

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

Thiazide diuretics and calcium containing preparations

Use with caution in patients being treated with thiazide diuretics or calcium containing preparations as they may have an increased risk of developing hypercalcaemia. Calcium levels should be monitored.

Other vitamin D containing preparations

Vitamin D or its analogous should not be given concurrently with alfacalcidol as may enhance the risk of hypercalcaemia.

Anticonvulsants

Patients taking barbiturates or anticonvulsants may require larger doses of Alfacalcidol to produce the desired effect due to the induction of hepatic detoxification enzymes.

Magnesium-containing antacids

Magnesium based antacids and laxatives should not be used during treatment with alfacalcidol due to increased risk of hypermagnesaemia.

Aluminium-containing preparations

Alfacalcidol 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 Alfacalcidol formulations. Alfacalcidol 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 are no adequate data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Therefore, Alfacalcidol is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

Although it has not been established, it is likely that increased amounts of 1,25-dihydroxyvitamin D will be found in the milk of lactating mothers treated with Alfacalcidol. This may influence calcium metabolism in the infant.

Because of inadequate data, lactation is advised against during treatment with alfacalcidol. Breast-fed infants of alfacalcidol-using mothers should be monitored closely for hypercalcaemia.

Fertility

There are no clinical studies on the effect of alfacalcidol 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 most frequently reported undesirable effects are 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.

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Excessive intake of Alfacalcidol 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

Pharmacotherapeutic group: Vitamin D and analogues. ATC code: A11CC03

Clinical efficacy and safety

Impaired 1α -hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D 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 Alfacalcidol.

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 Alfacalcidol 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

Absorption

In patients with renal failure, 1-5 microgram/day of 1α -hydroxyvitamin D (1α -OHD3) increased intestinal calcium and phosphorus absorption in a dose-related manner. This effect was observed within 3 days of starting the drug and conversely, it was reversed within 3 days of its discontinuation.

In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1 μ g 1α -OHD3 orally and usually peaked at 24 hours. 1α -OHD3 also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular re-absorption. This latter effect is a result of PTH suppression by 1α -OHD3. The effect of the drug on calcium was about double its effect on phosphorus absorption.

Distribution

Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving 1α -OHD3 in a dose of 0.5- 1.0 microgram/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

Biotransformation

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

5.3 Preclinical safety data

Chronic toxicity:

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.

Genotoxicity:

Alfacalcidol is not genotoxic.

Reproduction toxicity:

No specific effects of alfacalcidol on fertility or behaviour of the offspring were noted in rats and rabbits. In terms of embryo-fetal development, fetal 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

Citric acid, anhydrous All-rac- α -Tocopherol Propyl gallate, Ethanol, anhydrous Arachis oil, hydrogenated

The capsule shell contains:

Gelatin

Glycerol

Anidrisorb

Purified water

Medium chain triglyceride

The capsules contain the following colours:

0.5 microgram capsules: titanium dioxide (E171) and ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The finished products are Alfacalcidol 0.5 mcg capsules soft, to be marketed in white opaque HDPE container, with white opaque HDPE screw closure and induction sealing.

Pack size: 30 capsules, 50 capsules and 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2014

10 DATE OF REVISION OF THE TEXT

26/11/2018