

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AlfaD® 0.25 Microgram Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soft gelatin capsules containing alfacalcidol (1 α -hydroxyvitamin D₃) 0.25 microgram.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Oval, opaque reddish-brown, elastic soft gelatin capsule, imprinted “0.25” on one side with black ink, containing clear, pale yellow oily solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AlfaD® is used for treating conditions in which calcium metabolism is disturbed due to impaired 1 α -hydroxylation and other disorders associated with Vitamin D resistance.

The main indications are:

- Renal osteodystrophy
- Hypoparathyroidism
- Hyperparathyroidism (with bone disease)
- Nutritional and malabsorptive rickets and osteomalacia
- Hypophosphataemic Vitamin-D resistant rickets and osteomalacia
- Pseudo-deficiency (D-dependent Type I) rickets and osteomalacia
- Post-menopausal osteoporosis in patients who are unsuitable for/intolerant to treatment with a bisphosphonate
- Osteoporosis secondary to treatment with glucocorticoids in patients who are unsuitable for /intolerant to treatment with a bisphosphonate

4.2 Posology and method of administration

Route of administration: oral

Indications: *Renal osteodystrophy, hypoparathyroidism, hyperparathyroidism, rickets and osteomalacia:*

Starting dose: Children 20kg and over:	1 microgram/day
Adults:	1 microgram/day
Elderly patients:	0.5 microgram/day

The dose should subsequently be adjusted to avoid hypercalcaemia according to the biochemical response. Plasma calcium levels (preferably corrected for protein binding) should initially be measured weekly. The dose of AlfaD can be increased by increments of 0.25 to 0.5 micrograms/day. Most adults respond to doses of 1 to 3 micrograms/day. Once the dose is stabilised, calcium levels may be measured every 2-4 weeks.

Indices of response, in addition to plasma calcium, may include alkaline phosphatase, parathyroid hormone levels, bone radiography and histological investigations. When there is biochemical or radiographic evidence of bone healing (or in hypoparathyroidism when calcium levels have normalised) the dose required for maintenance generally decreases to around 0.25 to 1 microgram/day. Should hypercalcaemia occur, AlfaD should be stopped until plasma calcium returns to normal (usually about a week) then restarted at one half of the previous dose.

Renal Osteodystrophy - Patients with already high plasma calcium levels may have autonomous hyperparathyroidism. In this situation they may not respond to alfacalcidol and other therapeutic measures may be indicated.

In patients with chronic renal disease it is particularly important to check the plasma calcium frequently because prolonged hypercalcaemia may further impair renal function.

Before and during AlfaD treatment, the use of phosphate binding agents to prevent hyperphosphataemia may also be considered.

Hypoparathyroidism - Low plasma calcium levels may be restored to normal more quickly with AlfaD than with parent Vitamin D. Severe hypocalcaemia is corrected more rapidly with higher doses of AlfaD (eg 3-5 micrograms) together with calcium supplements.

Hyperparathyroidism - In patients needing surgery for primary or tertiary hyperparathyroidism, pre-operative treatment with AlfaD for 2-3 weeks can reduce bone pain and myopathy without aggravating hypercalcaemia. To decrease the risk of post-operative hypocalcaemia, AlfaD should be continued until the plasma alkaline phosphatase falls to normal or hypercalcaemia occurs.

Nutritional and Malabsorptive Rickets and Osteomalacia - Malabsorptive osteomalacia, which responds to large doses of IM or IV parent Vitamin D, will respond to small oral doses of AlfaD. Nutritional rickets and osteomalacia can also be rapidly cured with AlfaD.

Hypophosphataemic Vitamin D-Resistant Rickets and Osteomalacia - Normal doses of AlfaD rapidly relieves myopathy, when present, and increase calcium and phosphate retention. Phosphate supplements may also be required in some patients. Neither large doses of parent Vitamin D nor phosphate supplements are entirely satisfactory in these conditions.

Pseudo-Deficiency (D-Dependent Type I) Rickets and Osteomalacia - As with the nutritional conditions, similar oral doses of AlfaD are effective in circumstance which would require high doses of parent Vitamin D.

Osteoporosis

Adults including the elderly:

Treatment dose: 1 microgram/day

Serum calcium and creatinine levels should be determined at 1, 3 and 6 months, and at 6 monthly intervals thereafter.

The dose of AlfaD should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.

Use in Children

AlfaD® capsules are not indicated in children under 20kg as the dosage cannot be titrated adequately.

Use in Elderly

The clinical manifestations of hypo- or hyper calcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

4.3 Contraindications

Hypercalcaemia; metastatic calcification.

Alfacalcidol should not be used in patients with evidence of Vitamin D toxicity or known hypersensitivity to the effects of Vitamin D or any of its analogues. AlfaD capsules should not be used in patients with peanut allergy or hypersensitivity to any of the other ingredients.

4.4 Special warnings and precautions for use

Alfa-D should be used with caution for:

- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients
- patients with nephrolithiasis

Alfacalcidol increases the intestinal absorption of calcium and phosphate, serum levels of which should be monitored, particularly in children, patients with renal failure and patients receiving high doses.

To maintain serum phosphate at an acceptable level in patients with renal bone disease a phosphate binding agent may be used.

Hypercalcaemia may appear in patients treated with AlphaD, the early symptoms are as follows:

- polyuria
- polydipsia
- weakness, headache, nausea, constipation

- dry mouth
- muscle and bone pain
- metallic taste

If hypercalcaemia or hypercalciuria occur this can be corrected rapidly by stopping treatment with AlfaD and any calcium supplements until plasma calcium levels return to normal, usually in about a week. AlfaD may then be restarted at half the last dose used.

Response to alfacalcidol may be impaired if the diet is markedly deficient in calcium.

Healing of bone lesions often indicates a decreased requirement for AlfaD in which case appropriate dose adjustments should be made (see Posology and Method of Administration).

AlfaD capsules contain arachis oil (peanut oil) and should not be taken by patients known to be allergic to peanut. As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid AlfaD.

4.5 Interaction with other medicinal products and other forms of interaction

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias. Patients taking digitalis concurrently with alfacalcidol must therefore be closely monitored.

Patients on barbiturates or other anticonvulsants such as carbamazepine, phenytoin or primidone, may require an increased dose of AlfaD to produce the desired effect.

Absorption of alfacalcidol may be impaired by concurrent use of mineral oil (prolonged use), colestyramine, colestipol, sucralfate or large amounts of aluminium-based antacids.

Caution should be exercised in the use of magnesium-based antacids or laxatives for patients taking alfacalcidol who are on chronic renal dialysis. Hypermagnesaemia may occur.

The risk of hypercalcaemia is increased in patients taking calcium-containing preparations or thiazide diuretics concurrently with alfacalcidol.

Alfacalcidol is a potent derivative of Vitamin D. Pharmacological doses of Vitamin D or its analogues should not be given during alfacalcidol treatment because of the possibility of additive effects and an increased risk of hypercalcaemia.

4.6 Pregnancy and lactation

There is insufficient evidence on which to assess the safety of alfacalcidol use during pregnancy, although it has been widely used for many years without apparent adverse effects. Animal studies have not revealed any hazard but as with all drugs, AlfaD should only be used during pregnancy if treatment is essential and no better alternative is available.

Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Although not definitely established, it is likely that increased levels of 1,25-dihydroxyvitamin D₃ will be found in the breast milk of mothers treated with alfacalcidol. This might have an influence on calcium metabolism in a breast-fed infant.

4.7 Effects on ability to drive and use machines

AlfaD has no influence on the ability to drive or use machines.

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions.

Adverse effects generally relate to abnormally elevated serum calcium levels leading to symptoms of anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised plasma and urine concentrations of calcium and phosphate.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alpha-D treatment may then be re-started at half the previous dose.

In the case of renal impairment, elevated serum phosphate levels may be induced by AlfaD therapy. The dosage should be adjusted to the patient's requirements.

Also rarely nephrocalcinosis, pruritus, rash, urticaria.

4.9 Overdose

Excessive intake of Vitamin D leads to the development of hypercalcaemia. Administration of AlfaD should be stopped if hypercalcaemia occurs; symptoms of which include anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised plasma and urine concentrations of calcium and phosphate.

Severe hypercalcaemia may require treatment with general supportive measures.

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, biphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

In acute overdosage, early treatment with gastric lavage and/or the administration of mineral oil may reduce absorption and promote faecal elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: A11C C03 (Vitamin A and D, incl. combinations of the two, vitamin D and analogues).

Alfacalcidol is converted rapidly in the liver to 1,25dihydroxyvitamin 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 AlphaD and 1,25-dihydroxyvitamin D are very similar.

When 1- α hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D₃ production is reduced. Disorders in which this can occur include renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their

correction but will respond to small doses of AlfaD, which does not depend on the renal 1- α hydroxylation process.

When using parent Vitamin D, the high dose and variable response time makes dosage adjustment difficult. This can lead to unpredictable hypercalcaemia which may take many weeks, sometimes months, to reverse. With AlfaD, the more rapid onset of response allows better titration of dose and, if hypercalcaemia does occur, it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxy-vitamin D₃, the Vitamin D₃ metabolite which acts as a regulator of calcium and phosphate metabolism.

In patients with renal failure, 1-5 μ g/day of 1 α -hydroxyvitamin D (1 α -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 1 α -OHD3 orally and usually peaked at 24 hours. 1 α -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 1 α -OHD3. The effect of the drug on calcium was about double its effect on phosphorus absorption.

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

5.3 Preclinical safety data

There are no-preclinical data of relevance to the prescriber which are additional to that provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents

Citric Acid Anhydrous (E330)

Propyl Gallate (E310)

α -Tocopherol (E307)

Ethanol Anhydrous

Arachis Oil (peanut oil)

Soft Gelatin Capsule Shell

Gelatin

Glycerol 85% (E422)

Anidrisorb 85/70

Iron Oxide Red (E172)

Printing Ink Constituents

Shellac (54%) (E904)

Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottles of 30 or 100 capsules.

Cold form aluminium-aluminium blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 or 168 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited

Brampton Road

Hampden Park

Eastbourne

East Sussex

BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 0289/0459

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 January 2002 / 27 February 2009

10 DATE OF REVISION OF THE TEXT

04 March 2010