SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AlfaD 0.25 microgram capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soft capsule contains 0.25 micrograms of alfacalcidol (1 α-hydroxyvitamin D_3).

Excipients with known effect:

Each soft capsule contains up to 98.8 mg of arachis oil (peanut oil), up to 1.14 mg of ethanol (anhydrous), and up to 3.16 mg of sorbitol (part of Anidrisorb 85/70).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft (Capsule).

AlfaD 0.25 microgram soft gelatin capsules: Oval, opaque reddish-brown, elastic soft gelatin capsule, imprinted “0.25” on one side with black ink, containing a 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 1α-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 1) 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

Posology

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

The dose of AlfaD should subsequently be carefully adjusted to avoid hypercalcaemia according to the biochemical response of each individual patient. 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 of AlfaD 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 (e.g., 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.

Post-menopausal or Glucocorticoid-induced 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.

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 hypercalcaemia should be considered, especially in elderly patients with pre-existing renal or heart conditions.

Method of administration: oral

4.3 Contraindications

Hypercalaemia; metastatic calcification.

AlfaD 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 a peanut allergy or hypersensitivity to alfacalcidol or any of the other excipients listed in section 6.1.

4.4 Special warnings and precautions for use

AlfaD should be used with caution for:

- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead toarrhythmia in such patients
- patients with nephrolithiasis
- patients with granulomatous diseases, such as sarcoidosis, where sensitivity to vitamin D may be increased due to increased hydroxylation activity and vitamin D toxicity can occur.

AlfaD 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. Parathyroid hormone, alkaline phosphatase, and calcium x phosphate should be monitored as clinically indicated.

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

Hypercalcaemia may appear in patients treated with AlfaD, the signs/symptoms of which are listed in section 4.8.

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 AlfaD 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 withsoya allergy should also avoid AlfaD.

This medicinal product contains up to 3.16 mg of sorbitol as an excipient (see Anidrisorb 85/70 in list of excipients in section 6.1) and patients with rare hereditary problems of fructose intolerance (HFI) should not take it.

This medicinal product contains a small amount of alcohol (ethanol) (less than 2mg per soft capsule, corresponding to less than 1% [w/w]). The amount of alcohol (ethanol) in one soft capsule of this medicine is equivalent to less than 1 mL of beer or 1 mL of wine. The small amount of alcohol in this medicine has no noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac glycosides

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias. Patients taking digitalis concurrently with alfacalcidol must therefore be closely monitored (see warnings and precautions in section 4.4).

Anticonvulsants

Anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine, or primidone) have enzyme-inducing effects resulting in an increased metabolism of alfacalcidol. Patients taking anticonvulsants may therefore require larger doses of AlfaD.

Bile acid sequestrants

Concomitant oral administration of bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the intestinal absorption of AlphaD. AlphaD 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.

Aluminium-containing preparations

Absorption of aluminium-containing antacids may be enhanced by AlfaD so concomitant use of large amounts of aluminium-containing antacids may result in aluminium-related toxicity.

Mineral oil and sucralfate

Absorption of AlfaD may be impaired by concurrent use of mineral oil (prolonged use) and sucralfate.

Magnesium-containing preparations

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

Thiazide-diuretics and calcium-containing preparations

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

Other Vitamin D-containing preparations

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of AlfaD in pregnancy women.

Animal studies have shown reproductive toxicity at high doses. AlfaD is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

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 AlfaD. This might have an influence on calcium metabolism in a breast-fed infant; consequently, breast-fed infants of AlfaD-treated mothers should be closely monitored for hypercalcaemia.

Fertility

There are no clinical studies on the effect of AlfaD on fertility. Animal studies showed adverse effects on fertility at high doses.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse effects generally relate to abnormally elevated serum calcium levels (hypercalcaemia) leading to signs or symptoms that may include abdominal pain/discomfort, anorexia, asthenia, confusional state, dehydration, dry mouth, fatigue/lassitude, nausea, vomiting, constipation or diarrheoa, weight loss, muscle or bone pain, metallic taste, kidney stones, renal impairment, somnolence, sweating, headache, polyuria and polydipsia, 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). AlphaD 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.

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

- **Skin and subcutaneous tissue disorders**

  Common: Rash, Pruritus

  Not known: Urticaria

- **Renal and urinary disorders**

  Common: Hypercalciuria

  Uncommon: Nephrocalcinosis

- **General disorders and administration site conditions**

  Uncommon: Calcinosis (ectopic, or metastatic calcifications)

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 Google Play or Apple App Store.

4.9 Overdose

Excessive intake of Vitamin D leads to the development of hypercalcaemia (see section 4.8).

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, bisphosphonates, 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 1,25 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 AlfaD and 1,25dihydroxyvitamin 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 D_3, the Vitamin D_3 metabolite which acts as a regulator of calcium and phosphate metabolism.

In patients with renal failure, 1-5 μg/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 μg 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.

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 μg/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 Capsule Shell:

Gelatin
Glycerol 85% (E422)
Anidrisorb 85/70 (contains sorbitol (E420); sorbitan anhydrides; mannitol (E421); superior polyols)
Iron oxide yellow (E172)

Printing Ink Constituents:

Shellac (E904)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

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

Theramex Ireland Limited

3rd Floor, Kilmore House,
Park Lane,
Spencer Dock,
Dublin 1,
D01 YE64,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 49876/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 January 2002 / 27 February 2009

10 DATE OF REVISION OF THE TEXT

27/03/2025