1 NAME OF THE MEDICINAL PRODUCT

ALPHA D_3 0.25 mcg
ALPHA D_3 0.5 mcg
ALPHA D_3 1.0 mcg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alpha D3 0.25 mcg
Soft gelatin capsules containing 0.25 microgram of alfacalcidol

Alpha D3 0.5 mcg
Soft gelatin capsules containing 0.5 microgram of alfacalcidol

Alpha D3 1 mcg
Soft gelatin capsules containing 1 microgram of alfacalcidol

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 full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft gelatin.

Alpha D_3 0.25 mcg 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.

Alpha D_3 0.5 mcg soft gelatin capsules
Oval, opaque pale pink, elastic soft gelatin capsule, imprinted “0.5” on one side with black ink, containing a clear, pale yellow, oily solution.

Alpha D_3 1 mcg soft gelatin capsules
Oval, opaque cream to ivory, elastic soft gelatin capsule, imprinted “1.0” on one side with black ink, containing a clear, pale yellow, oily solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Renal bone disease (renal osteodystrophy)
- Hypoparathyroidism
- Hyperparathyroidism (with bone disease)- primary and tertiary.
- Rickets and osteomalacia.
- Osteoporosis

4.2 Posology and method of administration

General
The dosage and administration of Alpha D_3 should be adjusted according to the indication-specific notes.

Indications: renal bone disease (renal osteodystrophy), hypoparathyroidism, hyperparathyroidism (with bone disease)- primary and tertiary, rickets and osteomalacia.

The initial dosage is as follows:

Adults and children 20 kg and over bodyweight:	1 mcg/day
Elderly patients:	0.5 mcg/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 Alpha D_3 can be increased by increments of 0.25 to 0.5 mcg/day. Most adults respond to doses of 1 to 3 mcg/day. Once the dose is stabilised, calcium levels may be measured every 2-4 weeks.
Indices of response, in addition to a rise in 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 2 microgram/day. Should hypercalcaemia occur, Alpha D_3 should be stopped until plasma calcium returns to normal (usually about a week) then restarted at one half of the previous dose.

Renal Bone Disease (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 Alpha D_3 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 Alpha D_3 than with parent Vitamin D. Severe hypocalcaemia is corrected more rapidly with higher doses of Alpha D_3 (e.g., 3-5 mcg) together with calcium supplements.

Hyperparathyroidism
In patients needing surgery for primary or tertiary hyperparathyroidsim, pre-operative treatment with Alpha D_3 for 2-3 weeks can reduce bone pain and myopathy without aggravating hypercalcemia. To decrease the risk of post-operative hypocalcaemia, Alpha D_3 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 I.M. or I.V. parent Vitamin D, will respond to small oral doses of Alpha D_3. Nutritional rickets and osteomalacia can also be rapidly cured with Alpha D_3.

Hypophosphatemic Vitamin D-Resistant Rickets and Osteomalacia
Normal doses of Alpha D_3 rapidly relieve 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 Alpha D_3 are effective in circumstances which would require high doses of parent Vitamin D.

Osteoporosis

The recommended dosage in osteoporosis is 0.5 mcg/day. It should not be exceeded.

Serum calcium and creatinine levels should be determined at 1, 3 and 6 months, and at 6 monthly intervals thereafter.
The dose of Alpha D_3 should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.

Use in Children
Alfa D_3 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

- Alpha D3 capsules should not be used in patients with a peanut allergy or hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypercalcaemia.
- Metastatic calcification.
- Alpha D_3 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.

4.4 Special warnings and precautions for use

Alpha D3 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.
• 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.

Alpha D_3 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 phosphate binding agent may be used.

Hypercalcaemia may appear in patients treated with Alpha D_3, the signs/symptoms of which are listed in section 4.8.

If hypercalcaemia or hypercalciuria occur, this can be rapidly corrected by stopping treatment with Alpha D3 and any calcium supplements until plasma calcium levels return to normal, usually in about week. Alpha D_3 may then be restarted at half the last dose used.

Response to Alpha D_3 may be impaired if the diet is markedly deficient in calcium.

Healing of bone lesions often indicates a decreased requirement for Alpha D_3 in which case appropriate dose adjustments should be made (see Posology and method of administration).

Alpha D_3 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 Alpha D_3.

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 Alpha D_3 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 Alpha D_3.

Bile acid sequestrants
Concomitant oral administration of bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the intestinal absorption of Alpha D_3. Alpha D_3 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 Alpha D_3 so concomitant use of large amounts of aluminium-containing antacids may result in aluminium-related toxicity.

Mineral oil and sucralfate
Absorption of Alpha D3 may be impaired by concurrent use of mineral oil (prolonged use) and sucralfate.

Magnesium-containing preparations
Caution should be exercised in the concomitant use of magnesium-based antacids or laxatives for patients taking Alpha D_3 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 alfacalcidol.

Other Vitamin D-containing preparations
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 Fertility, Pregnancy and lactation

Pregnancy
There are no or limited data from the use of Alpha D3 in pregnant women. Animal studies have shown reproductive toxicity at high doses. Alpha D3 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 D_3 will be found in the breast milk of mothers treated with Alpha D_3. This might have an influence on calcium metabolism in a breast-fed infant; consequently, breast-fed infants of Alpha D_3 treated mothers should be closely monitored for hypercalcaemia.

Fertility
There are no clinical studies on the effect of Alpha D_3 on fertility. Animal studies showed adverse effects on fertility at high doses.

4.7 Effects on ability to drive and use machines

Alpha D_3 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 diarrhea, 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.

Hypercalcemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alpha D_3 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 Alpha D_3 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, 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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 fecal 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 Alpha D_3 and 1,25-dihydroxyvitamin D are very similar.

When 1-α hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D_3 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 Alpha D_3, 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 Alpha D_3, 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 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

Alpha D3 0.25mcg
Capsule contents
Arachis oil, ethanol dehydrated, propyl gallate, vitamin E (dl-α-tocopherol), citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70 (contains sorbitol; sorbitan anhydrides; mannitol; superior polyols; water), red iron oxide (E 172), edible ink black, purified water.

Alpha D3 0.5 mcg
Capsule Contents
Arachis oil, ethanol dehydrated, propyl gallate, vitamin E (dl-α-tocopherol), citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70 (contains sorbitol; sorbitan anhydrides; mannitol; superior polyols; water), titanium dioxide (E171), red iron oxide (E172), edible ink black, purified water.

Alpha D3 1.0 mcg
Capsule Contents
Arachis oil, ethanol dehydrated, propyl gallate, vitamin E (dl-α-tocopherol), citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70 (contains sorbitol; sorbitan anhydrides; mannitol; superior polyols, water), titanium dioxide (E171), yellow iron oxide (E172), edible ink black, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a dark place below 25°C.

6.5 Nature and contents of container

Alpha D_3 0.25 mcg:
Aluminium Blisters 10, 20, 30, 40, 50, 60, 100 Capsules.
Securitainer Plastic Bottles: 20, 30, 40, 50, 60, 100 Capsules.

Alpha D_3 0.5 mcg
Aluminium Blisters 10, 30 Capsules.
Securitainer Plastic bottles: 30, 100 Capsules.

Alpha D_3 1 mcg:
Aluminium Blisters: 10, 20, 30, 40, 50, 60, 100 Capsules.
Securitainer Plastic bottles: 20, 30, 40, 50, 60, 100 capsules.

Not all pack sizes and types may be marketed.

6.6 Special precautions for disposal

Not applicable

7 REGISTRATION HOLDER

Truemed Ltd, 10 Beni Gaon St., Poleg Industrial Park, P.O.Box 8105, South Netanya 4250499

8 MANUFACTURER

Theramex Limited ,Dublin, Ireland

9 REGISTRATION NUMBERS

Alpha D_3 0.25 mcg: 125 64 30474
Alpha D_3 0.5 mcg: 122 51 30212
Alpha D_3 1.0 mcg: 125 65 30475

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