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 alfacalcidol (1 α-hydroxyvitamin D_3) 0.25 microgram.

Alpha D3 0.5 mcg
Soft gelatin capsules containing alfacalcidol (1 α-hydroxyvitamin D_3) 0.5 microgram.

Alpha D3 1 mcg
Soft gelatin capsules containing alfacalcidol (1 α-hydroxyvitamin D_3) 1 microgram.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Alpha D_3 0.25 mcg
Oval, opaque reddish-brown, elastic soft gelatin capsule, imprinted “0.25” on one side with black ink, containing clear, pale yellow oily solution.

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

Alpha D_3 1 mcg
Oval, opaque cream to ivory, elastic soft gelatin capsule, imprinted “1.0” on one side with black ink, containing 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 which follow.

The initial dosage for all indications, excepting osteoporosis, is as follows:

Adults and children 20 kg and over bodyweight:	1 mcg/day
Elderly patients:	0.5 mcg/day

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

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
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 peanut allergy or ypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.

4.4 Special wanings 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.

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 Alpha D_3, 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 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 treatment 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 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.

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 Alpha D_3 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 Fertility, 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, Alpha D_3 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 D_3 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

Alpha D_3 has no influence on the ability to drive or use machines

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: 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).

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, diarrhea, weight loss, polyuria, sweating, headache, thirst, 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.

Also rarely nephrocalcinosis, pruritus, rash, urticaria.

Based on data from post-market use the total undesirable effect 'reporting rate' is rare or very rare being approximately 1:10,000 patients treated.

Metabolism and Nutrition Disorders

- Hypercalcaemia
- Hyperphosphataemia

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. Administration of Alpha D3 should be stopped if hypercalcaemia occurs; symptoms of which include anorexia, lassitude, nausea, vomiting, diarrhea, 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, 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, dehydrated alcohol, propyl gallate, dl- α- tocopherol, citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70, red iron oxide (E 172), printing ink black, purified water.

Alpha D3 0.5 mcg
Capsule Contents
Arachis oil, dehydrated alcohol, propyl gallate, dl- α- tocopherol, citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70, titanium dioxide (E171), red iron oxide (E 172), printing ink black, purified water.

Alpha D3 1mcg
Capsule Contents
Arachis oil, dehydrated alcohol, propyl gallate, dl- α- tocopherol, citric acid anhydrous.

Soft Gelatin Capsule Shell
Gelatin, glycerol 85%, anidrisorb 85/70, titanium dioxide (E171), yellow iron oxide (E 172), printing 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, 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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