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ALPHA D_3®
0.5 mcg Capsules

Composition
Each soft gelatin capsule contains:

Capsule Content
Active Ingredient
Alfacalcidol (1α-OHD_3) 0.5 mcg

Other Ingredients
Propyl gallate, alpha tocopherol, citric acid anhydrous, ethanol anhydrous, arachis oil (peanut oil).

Soft Gelatin Capsule Shell
Gelatin, glycerol, Anidrisorb 85/70 (sorbitol, mannitol, sorbitan, hydrogenation products of partly hydrolyzed starch, water), titanium dioxide (E171), red iron oxide (E172).

Mechanism of Action
Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxyvitamin D_3, the Vitamin D_3 metabolite which acts as a regulator of calcium and phosphate metabolism. Due to this rapid conversion, the therapeutic benefits of alpha D_3 (alfacalcidol) are virtually the same as those of 1,25-dihydroxyvitamin D_3.

The main effects are to increase circulating 1,25-dihydroxyvitamin D_3 levels, and thereby to increase intestinal absorption of calcium and phosphate, promote bone mineralisation, decrease plasma parathyroid hormone levels as well as to decrease bone resorption, with relief of bone and muscle pain.

25-hydroxylation of Vitamin D_3 by the liver is rarely impaired. However, when 1α-hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxylation D_3 production is reduced. Disorders in which this can occur include: renal bone disease, hypoparathyroidism, Vitamin D-dependent rickets and neonatal hypocalcemia. 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 1α-hydroxylation process. Additionally, Alpha D_3 treatment of intestinal calcium malabsorption associated with postmenopausal, senile and steroid-induced osteoporosis, improves the negative calcium balance of these patients. The more positive calcium balance, produced by Alpha D_3 treatment in osteoporotic patients, decreases bone loss and bone fracture rate.

When using parent Vitamin D, the high dose and variable response time can lead to unpredictable hypercalcemia 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 hypercalcemia does occur, it can be reversed within days of stopping treatment.

Indications
Alpha D_3 is used for treating conditions in which calcium metabolism is disturbed due to impaired 1α-hydroxylation, such as reduced renal function; in other disorders associated with Vitamin D resistance; and in calcium malabsorption of osteoporosis.

The indications are:

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

Contraindications

Alfacalcidol should not be administered in the presence of hypercalcemia, hyperphosphatemia (except when occurring with hypoparathyroidism) or hypermagnesemia.

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.

Warnings

Alfacalcidol should be used with caution for:

• patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients (see Drug Interactions).

• patients with nephrolithiasis.

Hypercalcemia may appear in patients treated with alfacalcidol, the early symptoms are as follows:

• polyuria
• polydipsia
• weakness, headache, nausea, constipation
• dry mouth
• muscle and bone pain
• metallic taste

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). Alpha D_3 treatment may then be restarted at a reduced dose (half the previous dose) {see also Precautions}.

Response to alfacalcidol may be impaired if the diet is markedly deficient in calcium. Healing of bone lesions often indicates a decreased requirement for AlphaD_3 in which case appropriate dose adjustments should be made.

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 this medicine.

Use in Pregnancy

There is insufficient evidence on which to assess the safety of alfacalcidol use during pregnancy. Animal studies are insufficient with respect to effects on pregnancy. The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcemia during pregnancy may produce congenital disorders in the offspring. Alpha D_3 should only be used during pregnancy if considered necessary by the physician.

Use in Breastfeeding

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 some influence on calcium metabolism in a breast-fed infant and discontinuation of breastfeeding should be considered.

Adverse Reactions

The most frequently reported undesirable effects are hypercalcemia, various skin reactions and, in the case of renal impairment, hyperphosphatemia which may be induced by alfacalcidol therapy. In hypercalcemic dialysis patients, the possibility of calcium influx from the dialysate should be considered.

Elevated serum calcium levels lead 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.

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
Hypercalcemia
Hyperphosphatemia

Skin and Subcutaneous Tissue Disorders
Pruritus
Rash
Urticaria

Renal and Urinary Disorders
Nephrocalcinosis
Renal impairment

No other side effects associated directly with alfacalcidol therapy have been noted.

Precautions

Alfacalcidol increases the intestinal absorption of calcium and phosphate, serum levels of which should be monitored, particularly in patients with renal failure, children 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. Throughout treatment with alfacalcidol, regular plasma and urinary (24-hour collection) calcium levels should be determined at weekly to monthly intervals depending on the progress of the patient. Frequent estimations are necessary in the early stages of treatment (particularly when the plasma calcium is already relatively high) and later when there is evidence of bone healing. Alfacalcidol therapy requires regular monitoring of calcium, phosphate, alkaline phosphatase, magnesium and creatinine levels as well as other appropriate biochemical parameters and should only be prescribed when suitable facilities to do so are available.

If there is biochemical evidence of bone healing (e.g., return towards normal serum alkaline phosphatase levels), hypercalcemia may develop if the dose of Alpha D_3 is not decreased appropriately. If hypercalcemia or hypercalciuria occur, this can be corrected rapidly by stopping treatment with Alpha D_3 and any calcium supplements until plasma calcium levels return to normal, usually in about a week. Alpha D_3 may then be restarted at half the last dose used.

Alfacalcidol should be administered with caution to patients with hypercalciuria, especially those with a history of renal calculi.

Drug Interactions

Alfacalcidol/Digitalis Glycosides: Hypercalcemia in patients taking digitalis preparations may precipitate cardiac arrhythmias. Patients taking digitalis concurrently with alfacalcidol must therefore be closely monitored.

Alfacalcidol/Barbiturates/Enzyme-inducing Anticonvulsant Drugs: Patients on barbiturates or other enzyme-inducing anticonvulsants may require an increased dose of Alpha D_3 to produce the desired effect.

Alfacalcidol/Drugs Affecting Intestinal Absorption: Absorption of alfacalcidol may be impaired by concurrent use of mineral oil (prolonged use), cholestyramine, colestipol, sucralfate or large amounts of aluminium-based antacids.

Alfacalcidol/Magnesium: Caution should be exercised in the use of magnesium based antacids or laxatives for patients taking alfacalcidol who are on chronic renal dialysis. Hypermagnesemia may occur.

Alfacalcidol/Calcium/Thiazides: The risk of hypercalcemia is increased in patients taking calcium-containing preparations or thiazide diuretics concurrently with alfacalcidol.

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

Effects on ability to drive and use machines

Alfacalcidol has no or negligible influence on the ability to drive or use machines

Dosage and Administration

General

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

Alpha D_3 capsules are not recommended for children under 20 kg bodyweight.

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
Neonates and premature infants:	0.05-0.1 mcg/kg/day
Children under 20 kg bodyweight:	0.05 mcg/kg/day

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

The dose should subsequently be adjusted to avoid hypercalcemia, 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.

In osteomalacic patients, the lack of rapid calcemia does not necessitate increasing the dosage. Other indices of response, such as plasma levels of alkaline phosphatase, may be more useful criteria for dose adjustment.

Indices of response, in addition to a rise in plasma calcium, may include a progressive reduction in alkaline phosphatase, a reduction in parathyroid hormone levels, an increase in urinary calcium excretion in patients with renal function, and an improvement in bone radiography and histology.

After normalisation of biochemical parameters, longer treatment periods may be required before radiological and histological improvements in bone defects can be observed. During the first weeks of therapy, improvement is often observed in clinical symptoms such as bone pain and myalgia. 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 mcg/day. Should hypercalcemia 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 Osteostrophy)

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 hypercalcemia may further impair renal function.

Before and during Alpha D_3 treatment, the use of phosphate binding agents to prevent hyperphosphatemia may also be considered.

Children with renal osteodystrophy seem to need relatively higher doses than adults and may even need the adult dose.

Hypoparathyroidism

Low plasma calcium levels can be dangerous and may be restored to normal more quickly with Alpha D_3 than with parent Vitamin D. Severe hypocalcemia 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 hypocalcemia, Alpha D_3 should be continued until the plasma alkaline phosphatase falls to normal or hypercalcemia occurs.

Neonate Hypocalcemia

The usual initial dose of Alpha D_3 is 0.05-0.1 mcg/kg/day (thereafter carefully titrated). Severe cases may require doses of up to 2 mcg/kg/day. Determination of plasma alkaline phosphatase levels may be more useful than plasma ionised calcium levels which may give guidance to response. Plasma alkaline phosphatase levels approximately 7.5 times greater than the adult range are indicative of active disease.

In early neonatal hypocalcemia, in premature infants, a dose of 0.1 mcg/kg/day of alfacalcidol has been shown to be effective.

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 parnet Vitamin D.

Osteoporosis

Malabsorption of calcium is a common feature of osteoporosis, whether postmenopausal, senile or steroid-induced. The decrease in intestinal calcium absorption is associated with low 1,25-dihydroxyvitamin D_3 levels, and can be normalised by small, probably physiological doses of orally administered alfacalcidol (0.5 mcg).

Improved calcium absorption is associated with an increase in urinary calcium, the magnitude of which is related to the dose of alfacalcidol and the dietary calcium intake. Accordingly, calcium supplementation is only recommended in osteoporotic patients if dietary intake is clearly inadequate.

Use in Elderly

Initiation of therapy requires a lower dose in elderly patients. The clinical manifestations of hypo- or hyper calcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

Overdosage

Manifestations

Hypercalcemia which may manifest clinically: as malaise, fatigue, weakness, dizziness, drowsiness, headache, anorexia, nausea, dry mouth, constipation, diarrhea, heartburn, vomiting, weight loss, polyuria, sweating, thirst, vertigo, abdominal pain or other gastrointestinal discomfort, muscle pain, bone pain, joint pain, pruritus or palpitations, and raised plasma and urine concentrations of calcium and phosphate.

Treatment

Administration of Alpha D_3 should be stopped if hypercalcemia occurs. 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.

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

Registration Number:

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Storage

Store in a dark place below 25°C.

Manufacturer

Teva Pharmaceutical Industries Ltd
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