For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ALPHA D3® CAPSULES 0.25 mcg/ 0.5 mcg

Alfacalcidol Capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION

ALPHA D3 0.25 mcg capsule:
Each soft gelatin capsule contains:
Alfacalcidol IP (1α-Hydroxyvitamin D3) 0.25 mcg
Colour: Ferric Oxide USPNF (Red) in capsule shells.

ALPHA D3 0.5 mcg capsule:
Each soft gelatin capsule contains:
Alfacalcidol IP (1α-Hydroxyvitamin D3) 0.5 mcg
Colours: Ferric Oxide USPNF (Red) and Titanium Dioxide IP in capsule shells.

PHARMACEUTICAL FORM

Soft gelatin capsules for oral administration

CLINICAL PARTICULARS

Therapeutic Indications

ALPHA D3 is indicated for the treatment of:

- postmenopausal osteoporosis
- senile osteoporosis with simultaneous vitamin D deficiency or the deficiency of its active metabolites,
- hypocalcaemia, especially in patients with illnesses leading to the impairment of vitamin D renal hydroxylation,
- rickets and osteomalacia resistant to vitamin D,
- hypoparathyroidism,
- renal osteodystrophy,
- disorders of calcium metabolism in patients with chronic renal failure,
- nephrotic syndromes in children after prolonged treatment with glucocorticosteroids,
- osteoporosis associated with glucocorticoid treatment.

Posology and Method of Administration

The dose of ALPHA D3 should be adjusted to avoid hypercalcaemia according to the biochemical response. Indices of response include plasma levels of calcium (ideally
corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Plasma levels should initially be measured at weekly intervals. The daily dose of ALPHA D3 may be increased by increments of 0.25 - 0.5 microgram. When the dose is stabilised, measurements may be taken every 2 - 4 weeks.

If hypercalcaemia occurs, ALPHA D3 should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

**Route of Administration**

For oral use.

**Adults**

Initial dosage for all indications for adults is 1 microgram/day. Most adult patients respond to doses between 1 and 3 micrograms/day. Maintenance doses are generally in the range of 0.25 to 1 microgram/day.

**Children**

Initial dosage for all indications is:
- children under 20 kg bodyweight 0.05 microgram/kg/day
- children over 20 kg bodyweight - 1 microgram/day

**Elderly**

Initial dosage for all indications for elderly is 0.5 microgram/day.

**Renal impairment**

Caution should be exercised when administering the product to patients with renal insufficiency (see Special Warnings and Special Precautions for Use).

**Hepatic impairment**

This medicinal product is contraindicated in patients with severe liver impairment (see Contraindications).

**Contraindications**

ALPHA D3 is contraindicated in:
- hypersensivity to the active substance or to any of the excipients,
- allergy to peanuts or soya beans,
- hypercalcaemia, metastatic calcification,
- hyperphosphatemia (with the exception of hyperphosphatemia in case of hypoparathyroidism),
Special Warnings and Special Precautions for Use

Calcium and phosphate metabolism

Therapy with alfacalcidol may lead to the excessive rise in calcium and phosphate concentrations in the blood serum. It is recommended to monitor the serum calcium and serum phosphate concentrations especially in the early stages of treatment. Calcium supplements may also be required. If examination results indicate hypercalcaemia, alfacalcidol should be discontinued until calcium concentrations return to normal levels. To maintain serum phosphates at an acceptable level in patients with renal bone diseases a phosphate binding agent may be used.

Concomitant disorders

Patients with renal failure, tertiary hyperparathyroidism or those on regular haemodialysis (potentially phosphates depleted) are particularly prone to develop hypercalcaemia. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. The early signs of hypercalcaemia are: polyuria, polydypsia, weakness, headache, nausea, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Therapy monitoring

During therapy with alfacalcidol it might be necessary (depending on the patient’s condition and risk factors) to determine plasma non-protein nitrogen, creatinine, alkaline phosphatase, the concentration of serum phosphates, calcium urine excretion and calcium/creatinine ratio in the second morning portion of urine (the calcium/creatinine ratio) every 1-3 months.

It is especially important to monitor calcium concentrations in patients with renal disorders. At the beginning of therapy, calcium concentrations should be measured once or twice a week; when the dose has been established they should be measured once a month. Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). Alfacalcidol may then be restarted at a reduced dose (half the previous dose). The use of alfacalcidol in the therapy of renal osteodystrophy requires systematic control of parathormone (PTH) concentration due to the risk of adynamic bone disease.

Diet

In patients on a low-calcium diet the effect of alfacalcidol may be reduced.
**Elderly**

In elderly patients it might be necessary to use lower doses of alfacalcidol.

**Other effects**

An autonomic hyperparathyroidism may appear in patients suffering from renal osteodystrophy who have high plasma calcium concentrations. Such patients may not react to alfacalcidol; in such circumstances other treatment methods have to be used.

Caution is necessary in patients treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients.

Caution should be paid to patients with nephrolithiasis.

Patients allergic to peanut or soya should not use this medicinal product (see **Contraindications**) as it contains arachis oil (peanut oil). Purified arachis oil may contain peanut protein.

**Interaction with Other Medicaments and Other Forms of Interaction**

**Cardiac glycosides**

Alfacalcidol increases the concentration of calcium in the plasma and therefore it also increases the toxicity of cardiac glycosides, which may lead to the risk of an overdose.

**Diuretics**

Thiazide diuretics, as well as medicinal products containing calcium taken systematically in an amount exceeding 1.5 g per day, increase the risk of hypercalcaemia.

**Antacids and milk-containing diet**

Antacids and regular consumption of large quantities of dairy products may lead to the milk-alkali syndrome and, in combination with alfacalcidol, to hypercalcaemia.

**Estrogens**

Products containing estrogens may increase the effects of alfacalcidol.

**Antacids**

Alfacalcidol increases the absorption of magnesium; when used simultaneously with antacids containing magnesium salts it may provoke hypermagnesemia. Antacids containing aluminium salts may provoke hypomagnesemia.
**Hydantoin, barbiturates and other anticonvulsant drugs**

The derivatives of hydantoin (e.g. phenytoin), barbiturates, prymidone and other anticonvulsant drugs may accelerate the conversion of vitamin D in the liver and may weaken the effects of alfacalcidol.

**Glucocorticosteroids**

Glucocorticoids reduce the effects of alfacalcidol.

**Salicylates**

Salicylates reduce the effects of alfacalcidol.

**Colestyramine, paraffin**

Colestyramine, colestipol and liquid paraffin may interfere with the intestinal absorption of alfacalcidol.

Since this medicinal product contains butylated hydroxytoluene it may interact with metal ions.

**Pregnancy and Lactation**

**Fertility**

There are no relevant data available.

**Pregnancy**

No systematic trials of alfacalcidol effect on pregnancy and the development of the foetus have been conducted so far. No similar trials have been conducted on experimental animals either. The trials of the effect on pregnancy and/or the development of the foetus and/or birth and/or postnatal development conducted on animals are insufficient. A potential risk for the human being is still unknown.

As hypercalcaemia during pregnancy may potentially produce congenital disorders in the offspring, alfacalcidol should not be used during pregnancy unless it is absolutely necessary.

**Lactation**

Alfacalcidol administered during lactation may lead to higher concentrations of calcitriol, which is an active metabolite, in the breast milk. Since higher than usual concentrations of calcitriol may influence calcium metabolism of the breastfed baby, alfacalcidol treatment should be discontinued for the duration of lactation as this may lead to the development of hypercalcemia in the infant.
Effects on Ability to Drive and Use Machines

There are no data that confirm any effect of alfacalcidol on the ability to drive vehicles or to operate machinery.

Undesirable Effects

Clinical Trial Data

Not relevant for this product.

Post Marketing Data

Adverse reaction frequency:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Immune system disorders

Not known: Hypersensitivity reactions (e.g. hypersensitivity in patients with asthma, skin irritation, contact dermatitis, irritation of conjunctiva)

Nervous system disorders

Not known: Headache, dizziness, confusional state (as a result of hypercalcaemia)

Metabolism and nutrition disorders

Not known: Hypercalcaemia, hyperphosphatemia (especially in patients with renal failure)

Cardiac disorders

Not known: Irregular heartbeat (associated with hypercalcaemia)

Gastrointestinal disorders

Not known: Diarrhoea, constipation, nausea, vomiting, dry mouth, polydipsia, irritation of mucous membranes including gastric mucosa, metallic taste (as a result of hypercalcaemia)

Skin and subcutaneous tissue disorders

Not known: pruritus, rash, urticaria
Musculoskeletal, connective tissue and bone disorders

Not known: Myalgia, bone pain (associated with hypercalcaemia)

Renal and urinary disorders

Not known: Hypercalciuria, polyuria, nephrocalcinosis, ectopic calcinations and renal impairment (as a result of hypercalcaemia)

General disorders and administration site conditions

Not known: Fatigue (associated with hypercalcaemia)

Undesirable effects of vitamin D and its derivatives are related to overdose of this medicinal product (see Overdose).

Overdose

Symptoms and Signs

The symptoms of vitamin D overdosage are as follows:

- hypercalcaemia,
- lack of appetite,
- thirst,
- nausea and vomiting,
- diarrhoea,
- polyuria,
- weakness,
- excessive sweating,
- headaches and dizziness.

In case of a major overdose on the verge of intoxication the following symptoms may appear:

- bone pain,
- ectopic calcification,
- proteinuria,
- arterial hypertension,
- cardiac arrhythmias.

Similar symptoms might be expected as a result of alfacalcidol overdose.

Prolonged continuous overdose of vitamin D may also lead (apart from the symptoms listed above) to general vascular and renal calcification as well as impairment of renal function.
Treatment

Hypercalcaemia is treated by suspending the administration of alfacalcidol. In severe cases of hypercalcaemia general supportive measures should be undertaken:

- hydration by intravenous infusion of saline (forced diuresis),
- electrolyte measurement,
- calcium and renal function assessment,
- electrocardiographic assessment especially for patients on digitalis.

More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Properties

Pharmacotherapeutic group

Vitamin D and analogues (ATC Code: A11CC03)

Mechanism of Action and Pharmacodynamic Effects

Vitamin D3, cholecalciferol, is converted by humans into an active metabolite, calcitriol, also known as a D hormone.

This conversion is effected through the process of 25-hydroxylation and 1-hydroxylation of cholecalciferol in the liver and kidneys. Since alfacalcidol is a 1-hydroxylate derivative, it can be activated to calcitriol only by means of hydroxylation in the liver. It is especially important in patients with renal dysfunction, since in their case hydroxylation in the renal tissue is impossible or impaired. Calcitriol produced as a result of the activation of cholecalciferol or alfacalcitriol is, together with parathormone and calcitonin, a basic factor regulating calcium metabolism in humans. Calcitriol intensifies the process of calcium uptake and distribution into the bones, provided that this element has been supplied adequately.

The receptor of the metabolically active form of vitamin D is present in the cells of many types of tissues, however the main organs in which its effects are most noticeable are the intestines, bones and kidneys.

Calcitriol triggers the processes which lead to the increase of serum calcium concentration through the intensification of the synthesis of Calcium Binding Protein (CaBP) which transports calcium from the gastrointestinal tract to the blood as well as the intensification of reabsorption of calcium in renal tubules.

Pharmacokinetic Properties

Absorption
Almost 100% of alfacalcidol is absorbed in the gastrointestinal tract.

**Distribution**

Pharmacokinetic data show that around 50% of an administered dose is converted into calcitriol, since the activity of 25-hydroxylase located in hepatocytes is regulated by the concentration of the substrate (alfacalcidol), the concentration of vitamin D-binding protein (DBP) and the concentration of the result of this conversion (calcitriol). The synthesis of calcitriol is intensified by a low serum calcium concentration and high concentration of parathormone. It is thought that owing to the above regulation processes the risk of overdose in patients who are administered alfacalcidol is lower than in patients who have received calcitriol. However, taking into account the toxicity of alfacalcidol, which is 2-3 times higher than the toxicity of calcitriol, the problem of intoxication due to an overdose has not yet been fully examined.

**Metabolism**

Calcitriol synthesized from alfacalcitriol appears in the blood plasma 25 minutes after administration and is transported by the blood plasma in the protein-bound form (DBP). The elimination half-life of calcitriol in the plasma is estimated as 3-5 hours. It does not, however, reflect the fall in the amount of this compound in the body, since the major part of the metabolite is present inside the cells in the receptor-bound form.

The elimination half-life of calcitriol in the body, corresponding to biological half-life, is estimated as app. 36 hours. Both alfacalcidol and calcitriol are mainly metabolised in the liver.

**Elimination**

A few inactive metabolites are eliminated in the urine (13%) and the faeces (the remaining amount).

**Special patient populations**

**Renal impairment**

Elimination is slower in dialysed patients; the elimination half-life in patients with peritoneal dialysis can even exceed 100 hours.

**Clinical Studies**

Not relevant for this product.

**Preclinical Safety Data**
LD50 of alfacalcidol in mice defined after a 24-hour examination of acute toxicity is 440 μg/kg in case of oral administration and 52 μg/kg in case of intravenous administration.

The median lethal dose LD50 of calcitriol in case of oral administration is 1350 μg/kg in mice and 620 μg/kg in rats; LD50 in case of intravenous administration in rats is 105 μg/kg.

In rats and rabbits the administration of alfacalcidol in doses of 0.3 and 0.9 μg/kg reduced the number and the neonatal weight of offspring; however it did not lead to any developmental disorders.

There are no preclinical data on the mutagenicity and carcinogenicity of this medicinal product.

PHARMACEUTICAL PARTICULARS

List of Excipients

**ALPHA D3 0.25 mcg :**

Citric acid (anhydrous), Propyl gallate, α-Tocopherol (E 307), Ethanol (anhydrous), Arachis oil refined

*Ingredients of capsule shell :* Gelatin, Glycerol, Sorbitol 70 per cent (non-crystallising), Ferric Oxide (Red)

**ALPHA D3 0.5 mcg :**

Citric acid (anhydrous), Propyl gallate, α-Tocopherol (E 307), Ethanol (anhydrous), Arachis oil refined

*Ingredients of capsule shell :* Gelatin, Glycerol, Sorbitol 70 per cent (non-crystallising), Ferric Oxide (Red), Titanium dioxide

Incompatibilities

There are no relevant data available.

Shelf Life

36 months

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store in a cool place.
Keep out of reach of children.

**Nature and Specification of Container**

*ALPHA D3 0.25 mcg:*

10 capsules in Aluminium-Aluminium blister strips; 3 strips in a carton.

*ALPHA D3 0.5 mcg:*

10 capsules in Aluminium-Aluminium blister strips; 3 strips in a carton.

All presentations may not be marketed in India.

**Instructions for Use/ Handling**

There are no special requirements for use and handling of this product.

**For further information please contact:**

GlaxoSmithKline Pharmaceuticals Limited,
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