New Zealand Data Sheet

Name of Medicine

One-Alpha®
alfacalcidol

Presentation

- One-Alpha® capsules 0.25 µg. White oval capsules with a joining seam around the middle and 8 mm in length.
- One-Alpha® capsules 1.0 µg. Smooth, brown oval capsules of 8 mm in length.
- One-Alpha® drops 2.0 µg/ml is a clear colourless solution.

Uses

Action

Alfacalcidol (1alpha-OHD3) is rapidly converted in the liver to 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3), the metabolite of vitamin D which acts as a regulator of calcium and phosphate homeostasis.

Impaired endogenous production of 1,25-dihydroxyvitamin D3 by the kidneys appears to contribute to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, and vitamin D-dependent rickets. These disorders, which require high doses of vitamin D for their correction will respond to small doses of One-Alpha®.

As compared to vitamin D, the main advantage of One-Alpha® is more rapid onset and offset of action. This allows a more accurate titration of dosage and decreases the risk of prolonged hypercalcaemia.

Pharmacokinetics

Serum levels of 1,25-(OH)2 D3 peak approximately 12 hours after a single dose of One-Alpha® and remain at measurable levels for at least 48 hours. The effect of 1 µg of One-Alpha® on calcium absorption has been observed within 6 hours and was maximal at 24 hours. The biological half-life is approximately 35 hours.

Indications

Disease caused by disturbances in the calcium metabolism in consequence of reduced endogenous production of 1,25-dihydroxyvitamin D3.

- Renal osteodystrophy.
- Postoperative or idiopathic hypoparathyroidism.
- Pseudohypoparathyrodism.
- As an adjunct to the management of tertiary hyperparathyroidism.
- Vitamin D-resistant rickets or osteomalacia.
- Vitamin D-dependent rickets, neonatal hypocalcaemia or rickets.
- Malabsorption of calcium.
- Malabsorptive and nutritional rickets and osteomalacia.
- Postmenopausal osteoporosis.
Dosage and Administration

Initial dose:
Adults and children above 20 kg body weight: 1 µg daily
Children under 20 kg body weight: 0.05 µg/kg/day
Neonates: 0.1 µg/kg/day
Dosage in the elderly: 0.5 µg/day

It is important to adjust dosage thereafter according to the biochemical responses and to avoid hypercalcaemia. Indices of response include levels of serum calcium, alkaline phosphatase, parathyroid hormone, urinary calcium excretion as well as radiographic and histological investigations. Patients with marked bone disease (other than those with renal failure) may tolerate higher doses without developing hypercalcaemia. However, failure of the serum calcium to rise promptly in osteomalacia patients does not necessarily mean that a higher dose is required since calcium from increased intestinal calcium absorption may be incorporated into demineralized bone. Most patients will respond to doses between 1 and 3 µg daily.

The dose requirements generally decrease in patients with bone disease when there is biochemical or radiographic evidence of bone healing and in hypoparathyroid patients after normal serum calcium levels have been attained. Maintenance doses are generally in the range of 0.25 to 1 µg daily.

In patients with osteoporosis receiving One-Alpha®, the recommended dosage for One-Alpha® for postmenopausal osteoporosis patients is 1 µg daily. The dose should be titrated according to the individual needs. Calcium supplementation should not be required if the normal dietary intake is in region of 1500 mg per day. However, many postmenopausal patients have dietary intake as little as 600 mg per day and calcium supplementation of 0.5 – 1 g per day could be required.

Patients currently taking barbiturates or other anticonvulsants may need larger doses of One-Alpha® to produce the desired effect.

Contraindications
Hypercalcaemia.

Hypersensitivity to alfacalcidol or any of the excipients listed in ‘Further Information’.

Warnings and Precautions

During the treatment with One-Alpha®, serum calcium and phosphate levels should be monitored regularly. PTH, alkaline phosphatase and calcium x phosphate should be monitored as clinically needed.

Plasma calcium levels should be measured 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.
Hypercalcaemia might appear in patients treated with One-Alpha®. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. Signs of hypercalcaemia are anorexia, fatigue, nausea and vomiting, constipation or diarrhoea, polyuria, sweating, headache, polydipsia, hypertension, somnolence and vertigo.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). One-Alpha® may then be restarted at a reduced dose (half the previous dose) with monitoring of calcium. The risk of hypercalcaemia depends on such factors as the degree of any mineralization defect, renal function, and the dose of One-Alpha®. Hypercalcaemia will occur when there is biochemical evidence of bone healing (e.g. a return towards normal in the level of plasma alkaline phosphatase) and the dose of 1alpha-OHD₃ is not reduced appropriately. Prolonged hypercalcaemia should be avoided as it may aggravate arteriosclerosis, cardiac valve sclerosis or nephrolithiasis. Transient or even long-lasting deterioration of kidney function has been observed.

One-Alpha® should also be used with caution in patients with calcification of pulmonary tissue as this may result in cardiac disease.

In patients with renal bone disease or severely reduced renal function One-Alpha® should be given in combination with a phosphate binding agent to prevent hyperphosphataemia and potential metastatic calcification.

One-Alpha® should be used with caution in patients with granulomatous diseases such as sarcoidosis where the sensitivity to vitamin D is increased due to increased hydroxylation activity.

Concurrent use of digitalis glycosides in the presence of hypercalcaemia due to vitamin D administration increases the potential for cardiac arrhythmias.

One-Alpha® capsules contain sesame oil as an excipient. Sesame oil may rarely cause severe allergic reactions.

One-Alpha® drops contain:
- 14% v/v ethanol (alcohol) as an excipient, that is, up to 340 mg ethanol per dose (corresponding to 6 µg of alphacalcidol), equivalent to 9 mL beer or 4.5 mL wine. The alcohol content may be harmful to those suffering from alcoholism. The alcohol content must be taken into account in pregnant or breastfeeding women, in children and in high-risk groups such as patients with liver disease or epilepsy.
- Sorbitol as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Methyl parahydroxybenzoate (also known as methyl hydroxybenzoate) as an excipient. Methyl parahydroxybenzoate may cause allergic reactions (possibly delayed).
- Macrogolglycerol hydroxystearate as an excipient. Macrogolglycerol hydroxystearate may cause stomach upset and diarrhoea.

**Effects on ability to drive and use machines**

Alfacalcidol has no or negligible direct influence on the ability to drive and use
machines. However, the patient should be informed that dizziness may occur during treatment and take this into account while driving or using machines.

**Pregnancy and lactation**

**Pregnancy**

There are limited data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity.

One-Alpha® should not be used in pregnancy unless clearly necessary as there is a risk that hypercalcaemia during pregnancy may produce congenital disorder in the offspring.

Caution should also be exercised when prescribing One-Alpha® to women of childbearing age.

**Breastfeeding**

Alfacalcidol is excreted in human milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain One-Alpha® therapy taking into account the benefit of breastfeeding for the child and the benefit of One-Alpha® therapy for the woman.

Breastfed infants of mothers taking One-Alpha® should be monitored closely for hypercalcaemia.

**Fertility**

There are no clinical studies on the effect of One-Alpha® on fertility.

**Adverse effects**

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and spontaneous reporting.

The most frequently reported undesirable effects are various skin reactions such as pruritus and rash, hypercalcaemia, gastrointestinal pain/discomfort and hyperphosphataemia.

Renal failure has been reported post-marketing.

Undesirable effects are listed by MedDRA system organ class (SOC) and the individual undesirable effects are listed starting with the most frequently reported one. Within each frequency grouping, adverse reactions are presented in the 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
<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Hypercalcaemia</td>
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<tr>
<td>Hyperphosphatemia</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Confusional state</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Headache</td>
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<td><strong>Rare</strong></td>
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<tr>
<td>Dizziness</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Abdominal pain and discomfort</td>
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<td><strong>Uncommon</strong></td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td>Vomiting</td>
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<td>Constipation</td>
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<tr>
<td>Nausea</td>
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<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Rash (various types of rash such as erythematous, maculo-papular and pustular have been reported)</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Myalgia</td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
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<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Hypercalciuria</td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Renal impairment (including acute renal failure)</td>
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<tr>
<td>Nephrolithiasis / Nephrocalcinosis</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Fatigue/asthenia/malaise</td>
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<tr>
<td>calcinosis</td>
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</tbody>
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**Paediatric population**

The observed safety profile is similar for children and adults.

**Interactions**

Concurrent use of thiazide diuretics or calcium containing preparations may enhance the risk of hypercalcaemia. Calcium levels should be monitored.

Concurrent use of other vitamin D containing preparations may enhance the risk of hypercalcaemia. Use of multiple vitamin D analogues should be avoided.

Anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine or primidone) have enzyme- inducing effects resulting in an increased metabolism of alfacalcidol. Patients taking anticonvulsants may require larger doses of One-Alpha®.
Absorption of magnesium-containing antacids may be enhanced by One-Alpha®, increasing the risk of hypermagnesaemia.

One-Alpha® may increase the serum concentration of aluminium. Patients taking aluminium containing preparations (e.g. aluminium hydroxide, sucralfate) should be monitored for signs of aluminium related toxicities.

Concomitant oral administration of bile acid sequestrants, such as cholestyramine, may impair the intestinal absorption of oral One-Alpha® formulations. One-Alpha® should be administered at least 1 hour before, or 4 to 6 hours after, the intake of the bile acid sequestrant in order to minimize the potential risk of interaction.

As outlined in the Warnings and Precautions section, the use of digitalis glycosides in the presence of hypercalcaemia due to vitamin D administration increases the potential for cardiac arrhythmias.

**Overdosage**

Excessive intake of One-Alpha® may lead to the development of hypercalcaemia, however, the effect is reversed rapidly on withdrawal. In severe cases of hypercalcaemia general supportive measures should be undertaken: Keep the patient well hydrated by IV infusion of saline (force diuresis), measure electrolytes, calcium, and renal functions indices, and assess electrocardiographic abnormalities, especially on patients using digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium contents should be considered.

**Pharmaceutical Precautions**

Capsules: Do not store above 25°C
Drops: Store at 2-8°C. Refrigerate, do not freeze.
One-Alpha® should be protected from light.

**Medicine Classification**

Prescription medicine.

**Package Quantities**

| Capsules 0.25 µg | 100 |
| Capsules 1.0 µg | 100 |
| Oral Drops 2µg/ml | 10ml and 20ml |

Not all package quantities may be available.
Further Information

List of Excipients

One-Alpha® capsules 0.25 µg: sesame oil, α-tocopherol, gelatin, glycerol (85 per cent), potassium sorbate, titanium dioxide.

One-Alpha® capsules 1 µg: sesame oil, α-tocopherol, gelatin, glycerol (85 per cent), potassium sorbate, red iron oxide (E172), black iron oxide (E172).

One-Alpha® oral drops: macrogolglycerol hydroxystearate (also known as polyoxyl 40 hydrogenated castor oil or polyethylene glycol hydrogenated castor oil), citric acid monohydrate, sodium citrate, sorbitol, α-tocopherol, methyl parahydroxybenzoate, anhydrous ethanol, purified water.

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