NEW ZEALAND DATA SHEET

1 ONE-ALPHA®

One-Alpha® 0.25 microgram capsules
One-Alpha® 1.0 microgram capsules
One-Alpha® 2 micrograms/mL oral drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One-Alpha® capsules contain either 0.25 microgram or 1.0 microgram of alfacalcidol.
One-Alpha® oral drops contain 2 micrograms/mL of alfacalcidol.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

One-Alpha® 0.25 microgram capsules: White oval capsules with a joining seam around the middle and 8 mm in length.

One-Alpha® 1.0 microgram capsules: Smooth, brown oval capsules of 8 mm in length.

One-Alpha® 2.0 microgram/mL drops is a clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Indications

Disease caused by disturbances in the calcium metabolism in consequence of reduced endogenous production of 1,25-dihydroxyvitamin D_3.

- 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.

4.2 Dosage and method of administration

Adults
Initial dose: 1 microgram/day

Elderly
Initial dose: 0.5 microgram/day

Paediatric Population
Initial dose:
Children above 20 kg body weight: 1 microgram/day
Children under 20 kg body weight: 0.05 microgram/kg/day
Neonates: 0.1 microgram/kg/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 microgram 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 microgam 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.

4.3 Contraindications

Hypercalcaemia.

Hypersensitivity to alfacalcidol or any of the excipients listed in section 6.1 List of excipients.

4.4 Special warnings and precautions for use

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-OHD_3 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 micrograms 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.

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, 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.

4.7 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.

4.8 Undesirable 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

Metabolism and nutrition disorders	
Common	Hypercalcaemia
	Hyperphosphatemia
Psychiatric disorders	
Uncommon	Confusional state
Nervous system disorders	
Uncommon	Headache
Rare	Dizziness
Gastrointestinal disorders	
Common	Abdominal pain and discomfort
Uncommon	Diarrhoea
	Vomiting
	Constipation
	Nausea
Skin and subcutaneous disorders	
Common	Rash (various types of rash such as erythematous, maculo-papular and pustular have been reported)
	Pruritus
Musculoskeletal and connective tissue disorders	
Common	Mylagia
Renal and urinary disorders	
Common	Hypercalciuria
Uncommon	Renal impairment (including acute renal failure)
	Nephrolithiasis / Nephrocalcinosis
General disorders and administration site conditions	
Uncommon	Fatigue/asthenia/malaise
	calcinosis

Paediatric population
The observed safety profile is similar for children and adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otage.ac.nz/reporting/

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Alfacalcidol (1alpha-OHD_3) is rapidly converted in the liver to 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$), the metabolite of vitamin D which acts as a regulator of calcium and phosphate homeostasis.

Impaired endogenous production of 1,25-dihydroxyvitamin D_3 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.

5.2 Pharmacokinetic properties

Serum levels of 1,25-$(OH)_2$ D_3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

One-Alpha® 2 microgram/mL oral drops: macrogolglycerol hydroxystearate (also known as polyoxyl 40 hydrogenated castor oil or polyethylene glycol hydrogenated castor oil), citric acid monohydrate, sodium citrate, sorbitol, dl-alpha tocopherol, methyl parahydroxybenzoate, anhydrous ethanol, purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Capsules: Do not store above 25°C
Drops: Store at 2-8°C. Refrigerate, do not freeze. Use within 4 months after opening.
One-Alpha® should be protected from light.

6.5 Nature and contents of container

Capsules 0.25 microgram	100
Capsules 1.0 microgram	100
Oral Drops 2 microgram/mL	10 mL and 20 mL

Not all package quantities may be available.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Link Pharmaceuticals Ltd.
Suite 32, Level 26
188 Quay Street
Auckland 1010
Telephone: +64 (9) 358 7146

9 DATE OF FIRST APPROVAL

Capsules: 21 August 1980
Oral drops: 03 October 2002

10 DATE OR REVISION OF THE TEXT

02 September 2021

Summary table of changes

Section changed	Summary of new information
8	Update to sponsor address

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