1.3.1.1 PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ONE-ALPHA CAPSULES 1 µg

ONE-ALPHA CAPSULES 0,25 µg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONE-ALPHA CAPSULES 1 µg

Soft gelatin capsules containing 1 µg of alphacalcidol (1 α-hydroxyvitamin D3)

ONE-ALPHA CAPSULES 0,25 µg

Soft gelatin capsules containing 0,25 µg of alphacalcidol (1 α-hydroxyvitamin D3)

Excipient with known effect: Sesame oil (99,9 mg)

Antioxidant: all-*rac*-α-Tocopherol (0,1 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ONE-ALPHA CAPSULES 1 µg

Brown-coloured and egg-shaped soft gelatin capsules

ONE-ALPHA CAPSULES 0,25 µg

Cream-coloured and egg-shaped soft gelatin capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Renal Bone Disease

b) Hypoparathyroidism

c) Hyperparathyroidism

d) Hypophosphataemic Vitamin D resistant rickets and osteomalacia

e) Pseudo-deficiency (D-dependent) rickets

f) Nutritional and malabsorptive rickets and osteomalacia

4.2 Posology and method of administration

Posology

Initial dose for all indications:

Adults and children over 20 kg bodyweight:	1 µg daily
Neonates and premature infants:	0,05 to 0,1 µg /kg/day
Children under 20 kg:	0,05 µg/kg daily

The dose of ONE-ALPHA should be adjusted thereafter 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 ONE-ALPHA may be increased by increments of 0,25 – 0,5 µg. When the dose is stabilised, measurements may be taken every 2 to 4 weeks.

Most adult patients respond to doses between 1 and 3 µg per day. When there is biochemical or radiographic evidence of bone healing, (and in hypoparathyroid patients when normal plasma calcium levels have been attained), the dose generally decreases. Maintenance doses are generally in the range of 0,25 to 1 µg per day. If hypercalcaemia occurs, ONE-ALPHA

should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

Hypoparathyroidism:

Low plasma calcium levels are restored to normal relatively quickly with ONE-ALPHA. Severe hypocalcaemia (e.g. after extensive neck surgery) may decline with higher doses of ONE-ALPHA (e.g. 3 to 5 µg) and calcium supplements. Normocalcaemia may be maintained with smaller doses within a relatively narrow dose range.

Hyperparathyroidism:

In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, pre-operative treatment with ONE-ALPHA for 2 to 3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia, ONE-ALPHA should be continued until plasma alkaline phosphatase levels fall to normal or hypercalcaemia occurs.

Hypophosphataemic vitamin D-resistant rickets and osteomalacia:

Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory, the latter tending to produce hypocalcaemia and hypoparathyroidism. ONE-ALPHA at normal dosage rapidly relieves myopathy when present and increases calcium and phosphorus retention and promotes bone healing. Phosphate supplements may also be required in some patients.

Pseudo-deficiency (D-dependent) rickets:

This requires large doses of vitamin D probably because of an inherited defect in the production of 1,25-$(OH)_2D_3$. ONE-ALPHA reverses this condition.

Nutritional and malabsorptive rickets and osteomalacia:

Nutritional rickets and osteomalacia can be cured with physiological doses of ONE-ALPHA. Patients with malabsorptive osteomalacia (responding to large doses of IM or IV vitamin D) will respond to small doses of ONE-ALPHA.

Neonatal hypocalcaemia:

For neonatal hypocalcaemia the normal starting dose of ONE-ALPHA is 0,05 to 0,1 µg/kg/day. Adjustment of the dose thereafter is by careful titration (but in severe cases doses of up to 2 µg/kg/day may be required). Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of plasma alkaline phosphatase may be markedly raised in the pre-term low birthweight infant. Whilst levels of 5 times the normal adult laboratory value may be usual in this group, alkaline phosphatase levels above 7,5 times the adult range indicate active disease. A dose of ONE-ALPHA of 0,1 µg/kg/day has proved effective as prophylaxis against early neonatal hypocalcaemia in premature neonates.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Hypercalcaemia.

Evidence of vitamin D intoxication.

First trimester of pregnancy

4.4 Special warnings and precautions for use

ONE-ALPHA should be given with care to patients with impaired renal function. If hypercalcaemia is induced by ONE-ALPHA it can be corrected by stopping treatment until

plasma calcium levels return to normal.

During treatment with ONE-ALPHA, serum calcium and serum phosphate levels should be monitored regularly especially in children, and in patients with renal impairment and patients receiving high doses. PTH, alkaline phosphatase and calcium phosphates should be monitored as clinically indicated. Facilities for monitoring plasma calcium and other appropriate biochemical parameters should be available when ONE-ALPHA is used.

Hypercalcaemia might appear in patients with normal renal function treated with ONE-ALPHA. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. Signs of hypercalcaemia are muscle and bone pain, muscle weakness, confusion, dehydration, anorexia, fatigue, nausea and vomiting, constipation or diarrhoea, polyuria, sweating, headache, polydipsia, hypertension, somnolence and vertigo.

In patients with normal renal function, hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal in about a week. ONE-ALPHA may then be restarted at half the previous dose with close monitoring of calcium.

Prolonged hypercalcaemia may aggravate arteriosclerosis, cardiac valve sclerosis or nephrolithiasis and therefore prolonged hypercalcaemia should be avoided when ONE-ALPHA is used in these patients. 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.

The risk of hypercalcaemia depends on such factors as the degree of any mineralisation defect, renal function and the dose of ONE-ALPHA that is used. Thus, hypercalcaemia is less likely in osteomalacia and more likely in renal failure. 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 ONE-ALPHA is not reduced appropriately. Prolonged hypercalcaemia should be avoided, particularly in chronic renal failure. 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 and later when there is evidence of bone healing. Plasma calcium levels should also be estimated regularly during the initial treatment of disorders without significant bone involvement, e.g. hypoparathyroidism.

In patients with renal bone disease or severely reduced renal function, a phosphate binding agent could be used simultaneously with alphacalcidol to prevent increased serum phosphate 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.

4.5 Interactions with other medicines and other forms of interaction

Thiazide diuretics and calcium containing preparations

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

Other vitamin D containing preparations

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

Anticonvulsants

Anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine or primidone) have enzyme-inducing effects resulting in an increased metabolism of alphacalcidol. Patients taking anticonvulsants may require larger doses of ONE-ALPHA.

Magnesium-containing antacids

Absorption of magnesium-containing antacids may be enhanced by ONE-ALPHA, increasing the risk of hypermagnesaemia.

Aluminium containing preparations

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.

Bile acid sequestrants

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of alphacalcidol in pregnant women. Studies in animals have shown reproductive toxicity at high doses.
ONE-ALPHA is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

Alphacalcidol is excreted in human milk. Mothers taking ONE-ALPHA should not breastfeed their infants. Consequently, breast-fed infants of alfacalcidol-using mothers 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

ONE-ALPHA 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

a. Summary of the safety profile

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.

b. Tabulated summary of adverse reactions

Undesirable effects are listed by MedDRA system organ class (SOC) and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common ≥1/10

Common ≥1/100 and < 1/10

Uncommon ≥1/1,000 and <1/100

Rare ≥1/10,000 and <1/1,000

Very rare <1/10,000

System organ class	**Frequency**	**Adverse Event**
Metabolism and nutrition disorders	Common	Hypercalcaemia Hyperphosphataemia
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 tissue disorders	Common	Rash* Pruritus

		*Various types of rash such as erythematous, maculopapular and pustular have been reported
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
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

Paediatric population

The observed safety profile is similar in 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8}

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

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, assess electrocardiographic abnormalities, especially on patient on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium contents should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamins: Other and ATC code: A11CC03

Alphacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin. 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 ONE-ALPHA and 1,25-dihydroxyvitamin D are very similar.

Impaired 1 a-hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and

vitamin D dependent rickets. These disorders, termed "vitamin D resistant" since they usually require high doses of vitamin D for their correction, respond to small doses of ONE-ALPHA.

The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of ONE-ALPHA is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

In patients with renal failure, 1 to 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 to 1,0 µg/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

5.3 Preclinical safety data

The non-clinical toxicity of alphacalcidol is attributed to the known vitamin D-effect of calcitriol on calcium homeostasis, which is characterised by hypercalcaemia, hypercalciuria and eventually soft tissue calcification.

Alphacalcidol is not genotoxic.

No specific effects of alphacalcidol on fertility or behaviour of the offspring were noted in rats and rabbits. In terms of embryo-foetal development, foetal toxicity (post-implantation loss, lower litter size and lower pup weight) was observed at doses high enough to cause toxicity in the dams. High doses of vitamin D are known to be teratogenic in experimental animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ONE-ALPHA CAPSULES 1 µg**:**

Excipients: Sesame oil

Antioxidant: All-*rac*-α-tocopherol

Capsule shell: Gelatin, glycerol, potassium sorbate, black iron oxide and red iron oxide.

ONE-ALPHA CAPSULES 0,25 µg**:**

Excipients: Sesame oil

Antioxidant: All-*rac*-α-tocopherol

Capsule shell: Gelatin, glycerol, potassium sorbate and titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ONE-ALPHA CAPSULES 1 µg**:** 36 months

ONE-ALPHA CAPSULES 0,25 µg**:** 36 months

6.4 Special precautions for storage

Capsules: Protect from direct sunlight and heat.

Store at or below 25 °C.

Keep out of reach of children.

6.5 Nature and contents of container

Tamper evident strip-blister pack of 30 capsules, consisting

of a push-through lid foil, a polyvinylchloride (PVC) form film and an aluminium laminate lidding material.

6.6 Special precautions for disposal

None

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.

1 Sabax Road,

Aeroton,

Johannesburg,

2013

Tel: +27 11 494 8000

8. REGISTRATION NUMBERS

ONE-ALPHA CAPSULES 1 µg**:**

M/22.1.4/0261

ONE-ALPHA CAPSULES 0,25 µg**:**

M/22.1.4/0262

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

ONE-ALPHA CAPSULES 1 µg**:** 15 June 1981

ONE-ALPHA CAPSULES 0,25 µg**:** 15 June 1981

10. DATE OF REVISION OF THE TEXT

13 June 2022

DETAILS OF REGISTRATION IN SSA COUNTRIES

ONE-ALPHA CAPSULES 1 µg**:**

NA: NS2 90/22.1.4/00192

BW: S2 B9300665

ONE-ALPHA CAPSULES 0,25 µg**:**

NA: NS2 90/22.1.4/00191

BW: S2 B9300660

Nadia Akbar Digitally signed by Nadia Akbar Date: 2022.06.28 13:07:03 +02'00'