APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ZODORAY 0,25 µg capsules

ZODORAY 0,5 µg capsules

ZODORAY 1 µg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZODORAY 0,25 µg capsules: Each capsule contains 0,25 µg alfacalcidol.

ZODORAY 0,5 µg capsules: Each capsule contains 0,50 µg alfacalcidol.

ZODORAY 1 µg capsules: Each capsule contains 1 µg alfacalcidol.

Excipient: Contains 98,7 mg arachis oil (peanut oil).

Contains sugar: Sorbitol 10 mg.

Contains traces of soya lecithin.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ZODORAY 0,25 µg capsules: Reddish brown coloured, oval shaped soft gelatine capsules containing clear oily liquid.

ZODORAY 0,5 µg capsules: Light pink coloured, oval shaped soft gelatine capsules containing clear oily liquid.

ZODORAY 1 µg capsules: Pale yellow coloured, oval shaped soft gelatine capsules containing clear oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Renal osteodystrophy

b) Hypoparathyroidism

c) Hyperparathyroidism (with bone disease)

d) Hypophosphataemic vitamin D resistant rickets and osteomalacia

e) Pseudo-deficiency (vitamin D-dependent) rickets

f) Nutritional and malabsorptive rickets and osteomalacia

4.2 Posology and method of administration

Posology

Initial dose for all indications

Adults:	1 µg daily
Children 20 kg body weight and above:	1 µg daily
Children less than 20 kg body weight:	0,05 µg/kg daily
Elderly:	0,5 µg daily

It is important to adjust dosage thereafter according to the biochemical responses and to avoid hypercalcaemia. Indices of response include levels of plasma calcium, alkaline phosphatase, parathyroid hormone, urinary calcium excretion as well as radiographic and histological investigations. Correct plasma levels should initially be measured at weekly intervals. The daily dose of Alfacalcidol may be increased by increments of 0,25 – 0,5 µg. When the dose is established, plasma levels of calcium, phosphorous and creatinine should be taken every 2 - 4 weeks.

Patients with marked bone disease may tolerate a higher dose without developing hypercalcaemia. However, failure of the plasma calcium to rise promptly in osteomalacic patients does not necessarily mean that a higher dose is required, since calcium from increased intestinal calcium absorption may be incorporated into demineralised bone. Most patients respond to doses between 1 to 3 µg daily.

The dose requirements generally decrease in bone disorders at a time when there is

biochemical or radiographic evidence of bone healing and in hypoparathyroid patients after normal plasma calcium levels have been attained. Maintenance doses are generally in the range of 0,25 to 1 µg daily.

Paediatric population

For neonatal hypocalcaemia the normal starting dose of 1α-OHD_3 is 0,05 to 0,1 µg/kg/day. Adjustment of the dose thereafter is by careful titration. 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 level 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.

4.3 Contraindications

- Hypersensitivity to Alfacalcidol, arachis oil (peanut oil), soya or to any of the excipients (see section 6.1)
- Hypercalcaemia or evidence of vitamin D intoxication.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

1α-OHD_3 should be given with care to patients with impaired renal function. If hypercalcaemia is induced by 1α-OHD_3 it can be rapidly corrected by stopping treatment Throughout treatment, regular plasma calcium determinations are essential. Facilities for monitoring regular corrected plasma calcium and other appropriate biochemical parameters should be available when 1α-OHD_3 is used.

Early symptoms include polyuria, polydipsia, weakness, headache, nausea, constipation, dry mouth, muscle and bone pain, metallic taste. If hypercalcaemia occurs, 1α-OHD_3 should be

stopped until the plasma calcium returns to normal (about one week) and then restarted at half the last dose used.

The risk of hypercalcaemia depends on such factors as the degree of any mineralisation defect, renal function, and the dose of 1α-OHD_3 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 1α-OHD_3 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.

Hypercalcaemia in conjunction with hyperphosphataemia increases the risk of metastatic calcifications. In diseases where hyperphosphataemia may occur, e.g. reduced kidney function, phosphate binding medicines should be used.

Patients concurrently taking barbiturates and other anticonvulsant medicines may require larger doses of 1α-OHD_3 to produce the desired effect, as these substances may induce the hepatic metabolising enzymes.

1α-OHD_3 should only be used during pregnancy and lactation if considered essential by the doctor.

ZODORAY contains arachis oil (peanut oil) and lecithin (soya lecithin). It you are allergic to peanut or soya, do not use this medicine.

Patients with rare hereditary problems of fructose intolerance should not take ZODORAY.

ZODORAY contains 1 mg of alcohol (ethanol) in each dosage unit which is equivalent to 1 % *v/v*. The small amount of alcohol in **[PRODCUT NAME]** will not have any noticeable effects.

4.5 Interaction 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 alfacalcidol. Patients taking anticonvulsants may require larger doses of **ZODORAY**.

Magnesium-containing antacids and laxatives: Absorption of magnesium-containing antacids may be enhanced by **ZODORAY**, increasing the risk of hypermagnesaemia.

Aluminium-containing preparations: ZODORAY 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 **ZODORAY**. **ZODORAY** should be administered at least 1 hour before, or 4 to 6 hours after the intake of the bile acid sequestrant in order to minimise the potential risk of interaction.

Alfacalcidol should be used with caution for:

a) Patients concomitantly treated with digoxin as hypercalcaemia may lead to dysrhythmia in such patients.

b) Patients with nephrolithiasis

4.6 Fertility, pregnancy and lactation

Pregnancy

ZODORAY should not be used in pregnancy. **ZODORAY** should not be used in the first

trimester of pregnancy.

Hypercalcaemia may produce congenital disorders.

There are no adequate data from the use of **ZODORAY** in pregnant women. Studies in animals have shown reproductive toxicity. The potential risks for humans are unknown.

Breastfeeding

Women using **ZODORAY** should not breastfeed their babies.

ZODORAY is suspected to be excreted into breast milk. Hypercalcaemia in the infant cannot be excluded. Because of inadequate data, breastfeeding is advised against during treatment with **ZODORAY**.

Fertility

There are no clinical studies on the effect of **ZODORAY** on fertility. A pre-clinical study did not show an effect on fertility in rats.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Frequent	Hypercalcaemia, hyperphosphataemia
Psychiatric disorders	Frequency unknown	Confusional state
Nervous system disorders	Less frequent	Headache, dizziness
Gastrointestinal disorders	Frequent	Abdominal pain and discomfort
	Less frequent	Diarrhoea, vomiting, constipation, nausea
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash* * Various types of rash such as erythematous, maculo-papular and pustular rash have been reported.
	Frequency unknown	Urticaria
Musculoskeletal and connective tissue disorders	Less frequent	Myalgia
Renal and urinary disorders	Frequent	Hypercalciuria
	Less frequent	Nephrolithiasis/Nephrocalcinosis
	Frequency unknown	Renal impairment
General disorders and administration site conditions	Less frequent	Fatigue, asthenia, malaise, calcinosis

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 Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The initial signs and symptoms of vitamin D intoxication associated with hypercalcaemia include weakness, fatigue, somnolence, headache, anorexia, nausea, vomiting, diarrhoea, and pruritus. If hypercalcaemia is allowed to persist, the following may also develop: conjunctivitis, a shortened Q-T interval and cardiac dysrhythmias, manifestations of impaired renal function consisting of polyuria, polydipsia, nocturia, hyposthenuria, dehydration and mild proteinuria. Agitation, apprehension, pain in the extremities, paralytic ileus, abdominal pain and, rarely, overt psychosis. Some mild elevations in AST and ALT have been reported in a small percentage of patients treated with **ZODORAY**.

Treatment of hypercalcaemia and overdosage in patients on haemodialysis:

General treatment of hypercalcaemia (greater than 0,25 mmol/l above the upper limit of the normal range) consists of immediate discontinuation of **ZODORAY** therapy, institution of a low calcium diet and withdrawal of calcium supplements.

General supportive measures: Keep the patient well hydrated by IV infusion of 0.9 % sodium chloride (forced diuresis), measure electrolytes, calcium and renal function indices; assess electrocardiographic abnormalities, especially in patients on digoxin.

Specific treatment: Glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content dialysis fluid.

Serum calcium levels should be determined daily until normocalcaemia ensues.

Hypercalcaemia frequently resolves in two to seven days. When serum calcium levels have returned to within normal limits, therapy may be reinstituted at a dose of 0,25 µg/day less

than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes and subsequent dosage titration. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 22.1.4 Vitamins: Other

Pharmacotherapeutic group: Vitamin D and analogues. ATC code: A11CC03

1α-hydroxyvitamin D_3 (1α-OHD_3) is converted in the liver to 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$), the metabolite through which vitamin D is considered to express most of its effects on calcium and phosphorus metabolism. Impaired endogenous production of 1,25-$(OH)_2D_3$ by the kidney appears to contribute to the disturbance in mineral metabolism found is several disorders including renal bone disease, hypoparathyroidism and pseudo-deficiency rickets. These disorders, termed "vitamin D resistant" since they usually require high doses of vitamin D for their correction, respond to small physiological doses of 1α-OHD_3

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. Should inadvertent hypercalcaemia occur it can be reversed by stopping treatment.

5.2 Pharmacokinetic properties

In patients with renal failure, 1-5 microgram/day of 1α-hydroxyvitamin D (1α-OHD_3) 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-OHD_3 orally and usually peaked at 24 hours. 1α-OHD_3 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-OHD_3. 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-OHD_3 in a dose of 0,5-1,0 microgram/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid,

All-rac-alpha-tocopherol (antioxidant),

Propyl gallate (antioxidant),

Anhydrous ethanol (1,0 % *v/v*),

Refined arachis oil (peanut oil).

Soft gelatine capsule shell:

Gelatine, glycerol,

Partially dehydrated sorbitol liquid (anidrisorb),

Purified water,

Medium chain triglyceride.

Lecithin (soya lecithin)

Capsule colours:

For 1 µg Capsules: Titanium dioxide (E171) and ferric oxide yellow (E172).

For 0,5 µg Capsules: Titanium dioxide (E171) and ferric oxide red (E172).

For 0,25 µg Capsules: Titanium dioxide (E171), ferric oxide red (E172) and ferric oxide black (E172).

Warning(s): Contains refined peanut oil, lecithin (soya lecithin), sorbitol and ethanol (1,0 % *v/v*).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years. Store at or below 25 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

White, opaque HDPE container with white opaque HDPE or polypropylene screw closure and induction sealing.

Pack sizes of 30's, 50's and 100's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd.

106 16th Road,

Building 2, Midrand

1685

Email: pv@trinitypharma.co.za

Contact number: +27 (0)10 594 5610

8 REGISTRATION NUMBER(S)

ZODORAY 1 µg	53/22.1.4/0677
ZODORAY 0,5 µg	53/22.1.4/0678
ZODORAY 0,25 µg	53/22.1.4/0679

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 March 2021

10 DATE OF REVISION OF THE TEXT

7 November 2024