PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ONE-ALPHA®

Alfacalcidol

Capsules, 1 and 0.25 mcg

Oral Drops, 2 mcg/mL

Injection, 2 mcg/mL

Vitamin D Analogue

[A11CC VITAMIN D AND ANALOGUES]

LEO Pharma Inc.
Thornhill, Ontario
L3T 7W8
www.leo-pharma.com/canada

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

ONE-ALPHA is indicated in adult patients with chronic renal failure for:

- management of hypocalcemia
- secondary hyperparathyroidism
- osteodystrophy

1.1. Pediatrics

Pediatrics: The safety and efficacy of ONE-ALPHA in children has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

2. CONTRAINDICATIONS

ONE-ALPHA is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- when there is biochemical evidence of hypercalcemia, hyperphosphatemia, or evidence of vitamin D overdose.

3. DOSAGE AND ADMINISTRATION

3.1. Dosing Considerations

ONE-ALPHA drops and capsules can be administered once daily with or without food and/or drink. The daily dose of ONE-ALPHA must be carefully individualized and titrated according to such factors as:

- The state of renal function
- Degree of bone mineralization
- Initial plasma calcium and alkaline phosphatase concentrations

Other factors which may be taken into account are urinary calcium excretion, plasma parathyroid hormone (PTH) and phosphorus. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests for additional information.

The success of treatment with ONE-ALPHA is also dependant on the patient receiving an adequate daily intake of calcium during treatment. The recommended daily allowance of calcium in adults is about 800-1000 mg (from all sources such as dialysate, diet and calcium supplements). The physician should ensure that each patient receives an adequate daily intake of calcium by prescribing a calcium supplement or instructing the patients in appropriate dietary measures. Calcium supplements should not exceed 500 mg of elemental calcium per day.

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3.2. Recommended Dose and Dosage Adjustment

Pre-Dialysis Patients on Daily Oral Therapy

Dose Titration: A dose of ONE-ALPHA that maintains serum calcium (adjusted for albumin concentration) within the normal range should be selected.

An initial dose of 0.25 mcg/day is recommended for the first 2 months, unless hypercalcemia develops. If hypercalcemia occurs then the dose should be reduced to 0.25 mcg on alternate days. If serum calcium is below the desired range, the dose may be adjusted in increments of 0.25 mcg/day every 2 months.

Maintenance Doses: Most patients will be maintained on a dose of 0.5 mcg/day. However, doses up to 1 mcg/day may be necessary to maintain serum calcium within the desired range.

Serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. If hypercalcemia develops at any time during treatment then the dose of alfacalcidol should be reduced by 50% and all calcium supplements stopped until calcium levels return to normal.

Dialysis Patients on Daily Oral Therapy

Dose Titration: The recommended initial dose of ONE-ALPHA is 1 mcg/day. If a satisfactory response in the biochemical parameters and clinical manifestations is not observed within 4 weeks, the daily dose may be increased by 0.5 mcg every 2 to 4 weeks. Most patients respond eventually to a dose of between 1 and 2 mcg/day. Only exceptionally, a dose of 3 mcg is required.

During this titration period, serum calcium levels should be obtained at least twice weekly and, if hypercalcemia is noted, the drug should be discontinued immediately until serum calcium levels normalize.

Maintenance Doses: Once serum calcium levels are normalized or only slightly reduced, the dose requirement of ONE-ALPHA generally decreases. Maintenance doses usually range from 0.25 - 1.0 mcg/day. If this small maintenance dose still proves too high, adequate control can usually be achieved by giving the dose on alternative days or even less frequently.

Serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. If hypercalcemia develops at any time during treatment then the dose of alfacalcidol should be reduced by 50% and all calcium supplements stopped until calcium levels return to normal.

Dialysis Patients on Intermittent Intravenous Therapy

Dose Titration: A dose of ONE-ALPHA that maintains total serum calcium in the upper half of the normal range should be selected. Calcium levels should be measured at least twice weekly during the dose titration period. The recommended initial dose of ONE-ALPHA is 1 mcg/dialysis (2-3 times weekly). If a satisfactory response in biochemical parameters is not observed within 1 week, the dose may be increased in weekly increments of 1 mcg/dialysis to a maximum of 12

mcg/week. The total dose titration period should not exceed 6 weeks. If hypercalcemia is noted, the drug should be discontinued immediately until serum calcium levels normalize. Once calcium levels return to the normal range, ONE-ALPHA should be re-introduced at lower doses.

Maintenance Doses: Doses required to maintain serum calcium levels in the upper half of the normal range are usually around 6 mcg/week but can range from 1.5 to 12 mcg/week. Serum calcium and phosphate levels should be monitored every other week or as is considered necessary if hypercalcemia is noted. If hypercalcemia develops, ONE-ALPHA should be discontinued immediately. Upon discontinuation of the drug, serum calcium levels generally normalize within a few days to a week. Calcium levels should be re-checked in another week and if still at normal levels, ONE-ALPHA may be re-instituted at half the previous dose.

See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests for additional information.

3.3. Administration

Instruct patients to when using the ONE-ALPHA Oral Drops, remove the protective cap but not the plastic dropper which is inserted into the bottle. To use the dropper, hold the bottle upside down. The liquid should flow immediately, but if it does not, tap the bottle gently. Do not shake the bottle.

3.4. Missed Dose

If a patient misses a dose, they should take the missed dose as soon as possible. However, if it is almost time for the next dose, then they should not double the dose.

4. OVERDOSAGE

Dosages of ONE-ALPHA in excess of daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. Conversely, a high intake of calcium and phosphate concomitantly with therapeutic doses of ONE-ALPHA may cause similar abnormalities.

Treatment of Hypercalcemia Due to Overdose

General treatment of serum calcium levels more than 1 mg/dL or 0.25 mmol/L above the upper limit of the normal range (usually 8.0 - 10.4 mg/dL or 2.2 - 2.6 mmol/L) consists of immediate discontinuation of ONE-ALPHA, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until the patient achieves normocalcemia. Hypercalcemia frequently resolves in 2 to 7 days. ONE-ALPHA therapy can be re-instituted at half the previous dose when serum calcium levels have returned to within normal limits. Serum calcium levels should be carefully monitored (at least twice weekly) during this period of dosage adjustment and subsequent dosage titration. Persistent or markedly elevated serum calcium levels in hemodialysis patients may be corrected by dialysis against a calcium-free dialysate.

In severe cases of hypercalcemia 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 patients using digitalis glycosides. More specifically, treatment with glucocorticosteroids, loop diuretics,

bisphosphonates, calcitonin and eventually haemodialysis with low calcium contents should be considered.

Treatment of Accidental Overdosage

The treatment of acute accidental overdosage with ONE-ALPHA should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium ion), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis glycosides. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short pharmacological action of ONE-ALPHA, further measures are probably unnecessary. However, if persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered depending on the underlying condition of the patient. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of dialysis against a calcium-free dialysate has also been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

5. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients	Description / Packaging
Oral			
	Capsules 0.25 mcg alfacalcidol/capsule	Sesame oil and all-rac-α-tocopherol; shell composition: gelatin, glycerol, potassium sorbate and titanium dioxide	Cream-coloured, egg-shaped soft gelatin capsules Available in tropical blisters of 100 (10x10 blisters).
	Capsules 1 mcg alfacalcidol/capsule	Sesame oil and all-rac-α-tocopherol; shell composition: gelatin, glycerol, potassium sorbate, red iron oxide E172 and black iron oxide E172	Brown egg-shaped soft gelatin capsules. Available in tropical blisters of 100 (10x10 blisters).
	Oral Drops 2 mcg alfacalcidol/mL 1 drop equals 0.1 mcg alfacalcidol.	Citric acid monohydrate, ethanol, macrogolglycerol hydroxystearate, methylparahydroxybenzoate, purified water, sodium citrate, sorbitol and all-rac-α-tocopherol	Clear or slightly opalescent colourless solution. Available in amber glass bottles of 10 mL fitted with a polyethylene dropping device.

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Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients	Description / Packaging
Intravenous	Liquid 2 mcg alfacalcidol/mL Each ampoule contains a unit dose of 1 mcg/0.5 mL or 2 mcg/1 mL.	Citric acid monohydrate 0.16 mg/ml, ethanol 80 mg/ml, sodium citrate 6.8 mg/ml, propylene glycol 415 mg/ml and water up to 1 ml	A sterile aqueous solution. Available in cartons of 10 ampoules.

6. WARNINGS AND PRECAUTIONS

General

The therapeutic margin with ONE-ALPHA is narrow, therefore, the optimal daily dose must be carefully titrated for each individual patient (See DOSAGE AND ADMINISTRATION).

ONE-ALPHA should not be used concomitantly with other vitamin D products or derivatives.

ONE-ALPHA is a potent cholecalciferol derivative with a profound positive effect on intestinal absorption of dietary calcium, which may lead to hypercalcemia. The occurrence of hypercalcemia depends on such factors as the degree of bone mineralization, the state of renal function and the dose of ONE-ALPHA. Excessive doses of the drug induce hypercalcemia and hypercalciuria.

The effect of ONE-ALPHA on inorganic phosphorus absorption is less marked than its effect on calcium, although it is important to recognize that the drug may increase plasma phosphorus concentrations, which may increase the requirements for phosphate binding agents.

Regular monitoring of plasma calcium is essential. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests for additional information.

Patients with renal bone disease and a relatively high initial plasma calcium and "autonomous" hyperparathyroidism are liable to early hypercalcemia, as are the minority of dialysis patients with low plasma alkaline phosphatase.

Cardiovascular

Prolonged hypercalcemia may aggravate arteriosclerosis or cardiac valve sclerosis and therefore prolonged hypercalcemia should be avoided when ONE-ALPHA is used in these patients. ONE-ALPHA should also be used with caution in patients with calcification of pulmonary tissue as this may result in cardiac disease.

In patients on digitalis glycosides hypercalcemia may precipitate cardiac arrhythmias. In such patients ONE-ALPHA should be used with extreme caution.

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Endocrine and Metabolism

As with all vitamin D preparations and metabolites, hypercalcemia must be anticipated when using ONE-ALPHA.

Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis or calcifications of the cornea or other soft tissues. During treatment with ONE-ALPHA, the Calcium-Phosphorus Product (Ca X P) (Ca = total serum calcium, mg/dL; P = serum inorgamic phosphate, mg/dL) should be maintained at accepted levels. A dialysate calcium level of 1.75 mmoles/L or above, in addition to excess dietary calcium supplements may lead to frequent episodes of hypercalcemia.

To control serum inorganic phosphate levels and dietary phosphate absorption, appropriate oral phosphate binding agents in association with a low phosphate diet may be necessary to prevent hyperphosphatemia and extra-skeletal calcifications. Serum phosphate levels were maintained below 2.0 mmol/L in the study that demonstrated the benefits of daily oral ONE-ALPHA on the development of bone disease in pre-dialysis patients.

Patients should be informed about the clinical symptoms connected with hypercalcemia. Signs of hypercalcemia are anorexia, fatigue, nausea and vomiting, constipation or diarrhoea, polyuria, sweating, headache, polydipsia, hypertension, somnolence and vertigo (see ADVERSE REACTIONS).

Monitoring and Laboratory Tests

Regular monitoring of plasma calcium is essential. Indeed, ONE-ALPHA should only be used when adequate facilities are available for monitoring of blood and urine chemistries on a regular basis. During treatment with ONE-ALPHA, progressive hypercalcemia either due to hyper-responsiveness or overdose may become so severe as to require emergency treatment. Hypercalcemia 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.

Laboratory tests considered essential to adequate patient monitoring include: serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase, creatinine, BUN and protein (for correction of plasma calcium in instances of hypercalcemia). For pre-dialysis patients treated with ONE-ALPHA, serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. For patients undergoing dialysis serum calcium should be determined at least twice weekly during dose titration. During maintenance therapy with ONE-ALPHA, 24-hour urinary calcium and phosphorus should be determined periodically.

Periodic ophthalmological examinations and radiological evaluation of suspected anatomical regions for early detection of ectopic calcifications are advisable.

Renal

The appearance of hypercalcemia is predicated on the ease with which calcium is utilized for bone mineralization and on renal excretion. Thus, chronic renal failure is a condition which

would dispose patients toward hypercalcemia.

Prolonged hypercalcemia may aggravate nephrolithiasis and therefore prolonged hypercalcemia should be avoided when ONE-ALPHA is used in these patients. Transient or even long-lasting deterioration of kidney function has been observed.

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

Sensitivity

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.

6.1. Special Population

6.1.1. Pregnant Women

ONE-ALPHA should not be used in pregnancy unless clearly necessary, as hypercalcemia during pregnancy may produce congenital disorders in the offspring. The safety of ONE-ALPHA in pregnant women has not been established.

Studies in animals have shown reproductive toxicity, which include reduced pregnancy rates, litter sizes and birth weights (see NON-CLINICAL TOXICOLOGY).

6.1.2. Breastfeeding

ONE-ALPHA may be excreted in human milk. Therefore, breast feeding during treatment should be avoided.

6.1.3. Pediatrics

The safety and efficacy of ONE-ALPHA in children has not been established.

A rise in plasma creatinine (or a fall in glomerular filtration rate) has been reported in children with renal failure who are treated with alfacalcidol. However, it is unclear whether this response was due to the action of the drug or to increased creatinine production during growth.

7. ADVERSE REACTIONS

7.1. Adverse Reaction Overview

In general, the adverse effects of ONE-ALPHA are similar to those encountered with excessive vitamin D intake.

Adverse reactions as listed by MedDRA system organ class (SOC) are as follows:

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Metabolism and nutrition disorders

Elevated blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, elevated aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT), anorexia, weight loss, polydipsia, hyperthermia, dry mouth, metallic taste

Cardiac disorders

Cardiac arrhythmia, hypertension

Eye disorders

Conjunctivitis, corneal calcification, photophobia

Infections and Infestations

Rhinorrhea

Psychiatric disorders

Overt psychosis

Nervous system disorders

Headache, somnolence, vertigo

Gastrointestinal disorders

Diarrhoea, vomiting, constipation, nausea, pancreatitis

Skin and subcutaneous tissue disorders

Pruritus

Musculoskeletal and connective tissue disorders

Muscle pain, bone pain, ectopic calcification

Renal and urinary disorders

Polyuria, nocturia

Reproductive system and breast disorders

Decreased libido

General disorders and administration site conditions

Fatigue, weakness

7.2. Post-Market Adverse Reactions

Hypercalcemia and possibly an exacerbation of hyperphosphatemia are the more frequent adverse reactions that have been reported with ONE-ALPHA in patients with renal osteodystrophy. Elevated levels of calcium and phosphorus increase the risk of metastatic calcification and may accelerate the decline in renal function in some patients with chronic renal failure.

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Metabolism and nutrition disorders: hypercalcaemia, hypercalciuria, hyperphosphatemia
Skin: rash
Gastrointestinal: abdominal pain, loss of appetite
Renal and urinary disorders: renal failure, kidney stones

8. DRUG INTERACTIONS

8.1. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or literature, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Established or Potential Drug-Drug Interactions

Proper/Common name	Effect	Clinical comment
Digitalis glycosides	Hypercalcemia may trigger cardiac arrhythmias	Calcium levels should be monitored
Mineral oil used as a laxative	May interfere with the intestinal absorption of ONE-ALPHA	ONE-ALPHA should be administered at least 1 hour before, or 4 to 6 hours after the intake of mineral oil in order to minimize the potential risk of interaction
Thiazide diuretics or calcium containing preparations	May enhance the risk of hypercalcemia	Calcium levels should be monitored
Vitamin D	May enhance the risk of hypercalcaemia	Use of multiple concurrent 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
Antacids containing magnesium	May contribute towards hypermagnesemia	Should be avoided
Aluminium containing preparations (e.g. aluminium hydroxide, sucralfate	ONE-ALPHA may increase the serum concentration of aluminium	Patients should be monitored for signs of aluminium related toxicities
Bile acid sequestrants such as cholestyramine	Oral administration may impare 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

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9. ACTION AND CLINICAL PHARMACOLOGY

9.1. Mechanism of Action

Alfacalcidol stimulates intestinal calcium and phosphorus absorption, the reabsorption of calcium from bone and possibly the renal reabsorption of calcium.

9.2. Pharmacodynamics

In the majority of patients treated with ONE-ALPHA, clinical symptoms of bone pain and muscle weakness begin to remit within 2 weeks to 3 months of the start of therapy. Malabsorption of calcium is rapidly corrected. In patients on daily oral therapy, plasma alkaline phosphatase and PTH levels generally begin to fall within 3 months, but plasma calcium levels may not normalize for several months. This delay should not necessarily be construed as a poor response but may indicate that calcium is being utilized for bone mineralization. The decrease in PTH levels may be more rapid in patients on intermittent intravenous therapy, with significant reductions being achieved within 3 months of therapy.

Hypercalcemia may occur at any stage of treatment, the risk being higher just after treatment is started and later when the plasma alkaline phosphatase level falls towards normal (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Because of a modest action on intestinal phosphorus absorption, ONE-ALPHA may elevate plasma phosphorus levels even further in patients with renal osteodystrophy and this may require increasing the dose of phosphate binding agents.

Normalization of plasma PTH levels frequently correlates well with healing of osteitis fibrosa, but radiographic improvement can occur without significant changes in plasma PTH concentrations. After 3 to 6 months of treatment, radiological evidence of healing is generally apparent. Histological responses, such as a decrease in the surface of bone undergoing resorption and a decrease in the volume of osteoid, are often much slower.

9.3. Pharmacokinetics

Absorption:
The biological half-life of alfacalcidol has been shown to be approximately 3 hours in the presence of renal insufficiency. However, serum levels of its active metabolite calcitriol peak approximately 12 hours after a single dose of oral ONE-ALPHA and approximately 4 hours after a single dose of intravenous ONE-ALPHA. Levels of calcitriol remain measurable for at least 48 hours. The effect of 1 mcg of oral ONE-ALPHA on intestinal calcium absorption has been observed within 6 hours of ingestion and was maximal at 24 hours.

Distribution:
There is evidence that vitamin D, its 1α-hydroxylated metabolites and analogues are extensively bound to a serum binding protein of the α -globulin fraction. Calcitriol appears to function in the intestine and bone by a receptor-nuclear activation mechanism.

Metabolism:
Vitamin D is itself biologically inactive and only expresses its physiological effects after undergoing two metabolic conversions. Before any physiological action can take place, vitamin D must first be hydroxylated at the 25 position in the liver to the metabolic intermediary 25-OHD_3. Secondly, 25-OHD_3 undergoes a 1α-hydroxylation in the kidney to the physiologically

active metabolite 1,25-$(OH)_2D_3$, referred to as calcitriol or 1,25-dihydroxy-vitamin D_3.
In contrast to Vitamin D, alfacalcidol is converted to calcitriol in the liver, effectively bypassing the critical renal metabolic conversion. This hepatic conversion of ONE-ALPHA is accomplished very rapidly, before any stimulation of the intestine or bone occurs. Impairment of the hepatic conversion of alfacalcidol to calcitriol is rare, even in the presence of liver abnormalities.

Special Populations and Conditions

Renal Insufficiency:
Conversion of 25-OHD_3 to calcitriol in the kidney becomes impaired or blocked in patients with renal failure or disorders of calcium and phosphorus metabolism. These patients respond poorly to even high doses of vitamin D. Hypocalcemia may lead to increased PTH secretion and high plasma PTH levels. Therefore, the patients with renal bone disease most likely to benefit from ONE-ALPHA therapy are those characterized by abnormally low plasma calcium levels, elevated alkaline phosphatase and PTH levels, and histological evidence of osteitis fibrosa and osteomalacia.

10. STORAGE, STABILITY AND DISPOSAL

0.25 mcg soft gel Capsules:	Protect from direct sunlight. Store at 15-25°C.
1 mcg soft gel Capsules:	Protect from direct sunlight. Store below 25°C.
Oral Drops:	Protect from direct sunlight. Keep refrigerated (2-8°C). Use within 4 months of first opening the bottle.
Intravenous Injection:	Keep ampoules in outer carton to protect from light. Keep refrigerated (2-8°C). Shake well before use. Single use ampoules - discard unused portion.

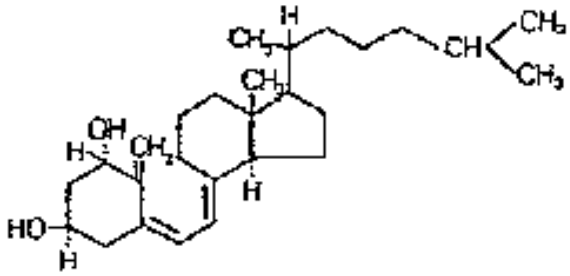
PART II: SCIENTIFIC INFORMATION

11. PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Alfacalcidol
(1α-hydroxyvitamin D_3 1α- hydroxycholecalciferol,
1α-hydroxyvitamin D_3, 1α-OHD_3)

Chemical Name: (5Z, 7E)-9,10-secocholesta-5,7,10(19)-triene-1α, 3β-diol
Molecular Formula: $C_{27}H_{44}O_2$
Molecular Mass: 400.65
Structural Formula:



Physicochemical Properties: Alfacalcidol is a colourless crystalline compound with a melting range of 136°-144°C. It is sensitive to light and very soluble in methanol, ethanol and chloroform, soluble in ether, sparingly soluble in methylformate and acetonitrile.

12. CLINICAL TRIALS

Pivotal Study:
The beneficial effects of ONE-ALPHA on the development of renal bone disease in pre-dialysis patients have been demonstrated in a large, randomized, placebo controlled study. Long-term administration of ONE-ALPHA (maximum dose of 1 mcg/day for up to 2 years) improved bone histology and halted the progression of changes in serum alkaline phosphatase activity and parathyroid hormone levels compared to placebo. Long-term administration of alfacalcidol proved to be well tolerated and had no adverse effect on renal function in patients for whom the dose was titrated to prevent persistent hypercalcemia. Although elevation of serum calcium was observed, marked hypercalcemia (> 3.00 mmol/L) was uncommon (4.5% of patients) and readily responded to decreases in drug dosage.

Non-Pivotal Studies:
In patients with renal failure, 1-5 mcg/day of alfacalcidol 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.

Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving oral alfacalcidol in a dose of 0.5 - 1.0 mcg/day. Serum calcium levels also increase during the first 4 weeks of treatment with intermittent (2-3 times weekly) intravenous alfacalcidol in a dose of 2.7-8.5 mcg/week. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1 mcg alfacalcidol orally and usually peaked at 24 hours. Alfacalcidol also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular reabsorption. This latter effect is a result of PTH suppression by alfacalcidol. The effect of the drug on calcium was about double its effect on phosphorus absorption.

13. NON-CLINICAL TOXICOLOGY

Non-clinical Pharmacology

In normal and anephric rats given 6.25 - 62500 pmol alfacalcidol and in the chick treated with 0.3-0.6 nmol alfacalcidol, the stimulation of intestinal calcium transport and bone mobilization was between one-half and equal to that of calcitriol. In both species, the conversion of alfacalcidol to calcitriol has been demonstrated by the isolation of radioactive calcitriol after administration of labelled alfacalcidol . Further studies on the transformation have demonstrated 25-hydroxylation in the liver homogenates from both the rat and the chick and also in intestinal mucosa from the chick. Whereas the hepatic 25-hydroxylation of vitamin D3 is feedback regulated, the corresponding conversion of alfacalcidol to calcitriol seems to be quantitative.

The 25-hydroxylation of alfacalcidol in the liver occurs very rapidly. Vitamin D-deficient rats were dosed with the radio-labelled compound (a single dose of 0.125 mcg 1α-OH(6-3H)D3 orally or i.v.). The intestinal calcium transport in orally dosed animals was noted after 4 hours and reached a maximum at 12 hours; in animals receiving the i.v. dose, there was insignificant intestinal calcium transport at 4 hours, but a maximal response was attained at 6 hours. Following both routes, a high level of transport was maintained for up to 96 hours. Intestinal tissue concentrations of 1,25-(OH)2 (6-3H)D3 appeared rapidly, within 2 hours of either the i.v. or oral dose of 1α-OH(6-3H)D3. These concentrations maximized by 4 hours at 310 and 250 pg/g following the oral and i.v. dose, respectively. Although intestinal levels of 1α-25(OH)2D3 are similar following a single oral or i.v. dose of alfacalcidol, blood and bone concentrations are much lower in the orally dosed animals than in animals dosed parenterally.

Blood levels and intestinal absorption of both alfacalcidol and calcitriol have also been determined in chicks following the oral or i.v. administration of 0.125 mcg 1α-OH(6-3H)D3 . As early as 1 hour after the i.v. injection, intestinal concentrations of 1,25-(OH)2 (6-3H)D3 were noted, which maximized at 6 hours. In orally dosed animals, no 1,25-(OH)2 (6-3H)D3 was measured at 1 hour, but at 4 hours the maximum concentration of 1.5 ng/g was reached which was 1.5 times higher than that reached after the i.v. dose. However, the i.v. dose yielded higher bone and blood concentrations than the oral dose.

These studies demonstrate that the transformation of alfacalcidol to calcitriol occurs rapidly enough to account for the biological response to alfacalcidol. Although it cannot be excluded that alfacalcidol may have a direct effect on the intestine when present at a relatively high concentration immediately after oral administration, it seems reasonable to conclude that it functions mainly after conversion to calcitriol .

Apart from these effects, alfacalcidol appears devoid of pharmacological action.

Acute Toxicity

Studies performed in mice and rats have revealed that alfacalcidol has an acute toxicity which is relatively low as compared to therapeutic doses. The following table illustrates the LD_{50} values obtained with both species: the discrepancy in the LD_{50} values reported by two centres are probably attributable to differences in the procedures followed in the two laboratories.

Mice died from 3 to 7 days after dosing by both routes of administration as a result of general calcification.

Rats treated orally with the drug showed progressive general deterioration and were highly emaciated at death. Autopsy revealed general calcification which was most pronounced in the kidneys.

Table 2. LD Values Obtained with 1α-Hydroxyvitamin D_3

SPECIES	ROUTE OF ADMINISTRATION	LD_{50} (mcg/kg)
Mice	Oral	490
Mice (Male)	Oral	476
Mice (Female)	Oral	440
Mice	I.V.	290
Mice (Male)	I.V.	71
Mice (Female)	I.V.	56
Rats	Oral	510
Rats (Male	Oral	340
Rats (Female)	Oral	720

Oral Subacute Toxicity

One study in rats showed that repeated dosing with up to 2.5 mcg/kg/day for 30 days did not cause any untoward effects. Higher doses resulted in hypercalcemia and metastatic calcification.

In another study, rats were dosed with 0.4, 2.0 and 10 mcg/kg/day of the drug for 7-8 weeks. From week 3 onwards, the animals showed signs of general deterioration, apathy and weight loss. Post-mortem examinations revealed a lighter colour and calcinosis in the kidneys in the highest dose group. In the other groups, there was a slight but dose-related calcinosis in the kidneys which was more pronounced in the females than in the males.

Dogs were treated orally for 3 to 8 weeks with alfacalcidol in doses of 0.1, 0.4 and 3.2 mcg/kg/day. After 3 and 7 weeks respectively, dogs on the 3.2 mcg dose and dogs on the 0.4 mcg dose showed considerable deterioration with loss of appetite and weight, apathy and subnormal temperature. Post-mortems revealed slight muscular dehydration and reduced fat deposition. Females on 0.4 mcg/kg/day had scattered small foci of calcium deposits and groups of dilated tubules in the cortex and medulla; the male animals, however, showed only traces of calcium deposition. In all 4 dogs on the highest dose, focal groups of dilated tubules with flattened epithelium and interstitial fibrosis in the cortex and medulla of the kidney were observed. Scattered calcium deposits were present in the fundus of the stomach (mucosa and submucosa) and in the bronchi and alveoli and corresponding vessels. In the group of dogs (2 male and 2 female) treated with 0.1 mcg/kg, histopathology showed one case of calcium deposits in the renal medulla. No other untoward effects were noted in the low dose group.

Intravenous Subacute Toxicity

In a 6 week study in rats dosed with 0.1, 0.3 and 0.9 mcg/kg/d of alfacalcidol, the only dose-effect relationship observed was for hemoglobinurea. Animals in the highest dose group exhibited cessation of growth followed by slight weight loss, languid behaviour, moderate reductions in food consumption, hypothermia, and pale mucous membranes. Pigmented corneal granulations were evident and post-mortem examinations showed weight reductions for the pituitary, ovaries and uterus. Renal tubule casts were also present and there was an increase in the intensity of renal microcalculi in females. In the control group receiving vehicle injections, there was slight hyperuremia and small increases in hemoglobinuria.

Sensitivity to vehicle injections was also noted in a 14 day tolerance study in beagle dogs. Dogs receiving high doses of vehicle (0.4 ml/kg) showed a slight degree of hemolysis immediately after injection which disappeared within 4 hours. In a 6 week study in dogs dosed with 0.01, 0.03, 0.09, and 0.18 mcg/kg/day of alfacalcidol, effects were noted only in the highest dose group. Aside from increases in monocyte number, post-mortem examinations showed vascular calcification and dystrophic mineralization in the aorta and stomach. Kidneys had a firmer texture, the kidney cortex zone had a paler colour, tubules were dilated and had chronic inflammatory cell infiltration.

Chronic Toxicity

Rats were dosed orally with 0.2, 0.8 and 3.2 mcg/kg/day with alfacalcidol for 6 months. Increased serum levels of calcium were recorded in all groups from week 9 onwards; phosphate levels were increased in week 26 and there was a decrease in total protein with the two highest dose levels at the end of the study. Autopsy revealed soft tissue calcification in the kidneys, stomach and aorta with the intermediate and high dose levels. A slight increase in the incidence of calcinosis of the kidney was observed in the low dose group.

In a 6-month study in dogs, the initial oral doses of alfacalcidol were 0.05, 0.1 and 0.2 mcg/kg/day, but because of adverse effects on bodyweight and food consumption, dosing with 0.2 mcg/kg/day was stopped after 72 days. In some of these animals, dosing continued at 0.025 mcg/kg/day which allowed the animals to recover. Apart from the effects with the 0.2 mcg dose, there were no untoward clinical signs or effects on bodyweight or food consumption. The only macroscopic abnormality noted was enlarged spleens in the treated dogs. Two dogs which were sacrificed after the 0.2 mcg/kg dose and 2 other dogs on 0.1 mcg/kg showed areas of dilated

basophilic tubules in the kidneys. One dog on 0.2 mcg/kg had numerous calcified foci in the lamina propria of the fundus and excessive muscle stiffness due to soft tissue calcification. Soft tissue calcification was also noted in a dog treated with 0.1 mcg/kg/day.

Teratogenic Studies

Studies were performed in rats and rabbits using daily doses of 0.1, 0.3 and 0.9 mcg/kg of alfacalcidol. Parent animals dosed with the drug had a lower weight gain than undosed animals. Reduced litter size and lower weights of fetuses were recorded in rabbits at the intermediate and high dose levels, but no significant increase in the incidence of fetal malformations were noted.

The effect of alfacalcidol on the reproductive function in the rats was investigated using the same doses. At the highest dose level, the pregnancy rate, litter size and birth weights were significantly lower than in control animals, in both the original parent animals and offspring of the first generation. No other parameters were affected and no late effects of the drug were observed in any of the progeny.