SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 1.0 microgram Capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol 1.0 microgram capsule, soft: Each soft capsule contains 1.0 microgram alfacalcidol

Excipient:

Alfacalcidol 0.5 microgram capsule, soft: Each soft capsule contains: 98.7 mg Arachis oil (peanut oil),

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Alfacalcidol 1.0 mcg Capsule, soft (capsule): Pale yellow coloured, oval shaped soft gelatin capsules containing clear oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfacalcidol is indicated in conditions where there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation such as when there is reduced renal function. The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Neonatal hypocalcaemia
e) Nutritional and malabsorptive rickets and osteomalacia
f) Pseudo-deficiency (D-dependent) rickets and osteomalacia
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia

4.2 Posology and method of administration

Route of administration: oral

Initial dose for all indications:

Adults:	1.0 microgram/day
Dosage in the elderly:	0.5 microgram/day
Neonates and premature infants:	0.05 - 0.1 microgram/kg/day
Children under 20 kg bodyweight:	0.05 microgram/kg/day
Children over 20 kg bodyweight:	1 microgram/day

The dose of Alfacalcidol 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 Alfacalcidol may be increased by increments of 0.25 - 0.5 microgram. When the dose is established, plasma levels of calcium, phosphorous and creatinine should be taken every 2 - 4 weeks.

Most adult patients respond to doses between 1and 3 micrograms 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 microgram per day. If hypercalcaemia occurs, Alfacalcidol should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

(a) Renal bone disease:

Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to Alfacalcidol Capsule, soft. Other therapeutic measures may be indicated.

Before and during treatment with Alfacalcidol Capsule, soft, phosphate binding agents should be considered to prevent hyperphosphataemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

(b) Hyperparathyroidism:

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

to normal or hypercalcaemia occurs.

(c) Hypoparathyroidism:

In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with Alfacalcidol. Severe hypocalcaemia is corrected more rapidly with higher doses of Alfacalcidol (e.g. 3-5 micrograms) together with calcium supplements.

(d) Neonatal hypocalcaemia:

Although the normal starting dose of Alfacalcidol is 0.05-0.1 microgram/kg/day (followed by careful titration) in severe cases doses of up to 2 microgram/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 alkaline phosphatase approximately 7.5 times above the adult range indicates active disease.

A dose of 0.1 microgram/kg/day of Alfacalcidol has proven effective as prophylaxis against early neonatal hypocalcaemia in premature infants.

(e) Nutritional and malabsorptive rickets and osteomalacia:

Nutritional rickets and osteomalacia can be cured rapidly with Alfacalcidol. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of Alfacalcidol.

(f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:

Although large doses of parent vitamin D would be required, effective doses of Alfacalcidol are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

(g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:

Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with Alfacalcidol at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

4.3 Contraindications

Hypercalcaemia,
Hypersensitivity to alfacalcidol, Arachis oil (peanut oil) or any of the other ingredients listed in section 6.1

4.4 Special warnings and precautions for use

During treatment with alfacalcidol plasma calcium, phosphate and

creatinine should be monitored frequently (see section 4.1).

Alfacalcidol should be used with caution for:

- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients
- patients with nephrolithiasis

During treatment with Alfacalcidol serum calcium and serum phosphate should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses. To maintain serum phosphate at an acceptable level in patients with renal bone disease a phosphate binding agent may be used.

Hypercalcaemia may appear in patients treated with Alfacalcidol the early symptoms are as follows:

- polyuria polydipsia
- weakness, headache, nausea, constipation dry mouth
- muscle and bone pain metallic taste

In case of hypercalcaemia alfacalcidol treatment should be stopped until serum calcium concentrations return to normal, usually in about 1 week. Alfacalcidol may then be restarted at half the last dose used**.**
Hypercalcaemia in conjunction with hyperphosphataemia increases the risk of metastatic calcifications. In diseases where hyperphosphataemia may occur, e.g. reduced kidney function, phosphate binding agents should be used.

Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias.

Patients taking barbiturates or anticonvulsants may require larger doses of Alfacalcidol to produce the desired effect due to the induction of hepatic detoxification enzymes.

Concomitant administration of colestyramine may interfere with the intestinal absorption of alfacalcidol.

Use with caution in patients being treated with thiazide diuretics as they may have an increased risk of developing hypercalcaemia.

Magnesium based antacids and laxatives should not be used during treatment with alfacalcidol due to increased risk of hypermagnesaemia. Vitamin D or its analogous and calcium or calcium containing preparations should not be

given concurrently with alfacalcidol.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no adequate data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.
Alfacalcidol should not be used during pregnancy unless clearly necessary.

Lactation:
Alfacalcidol is suspected to be excreted into breast milk. At high doses, hypercalcaemia in the infant cannot be excluded. Because of inadequate data, lactation is advised against during treatment with alfacalcidol.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions. Symptoms of hypercalcaemia are headache, weakness, anorexia, weight loss, nausea, vomiting, diarrhoea, constipation, polyuria, polydepsia, and muscle and bone pain, and metallic taste. Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alfacalcidol treatment may then be re-started at half the previous dose.

Based on data from post-market use the total undesirable effect 'reporting rate' is rare or very rare being approximately 1:10,000 patients treated.

- **Metabolism and Nutrition Disorders**
  Rare (≥1/10,000 to <1/1,000):
  Hypercalcaemia
  Hyperphosphataemia

- **Skin and Subcutaneous Tissue Disorders**
  Very rare (<1/10,000):
  Pruritus
  Rash
  Urticaria

- **Renal and Urinary Disorders**

Very rare (<1/10,000):
Nephrocalcinosis
Renal impairment

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Hypercalcaemia is treated by suspending the administration of Alfacalcidol.

In severe cases of hypercalcaemia general supportive measures should be undertaken. Keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal function indices; assess electrocardiographic abnormalities, especially in patients on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Impaired 1α-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, which require high doses of parent vitamin D for their correction, will respond to small doses of Alfacalcidol.

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 Alfacalcidol 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.

In patients with renal failure, 1 - 5 microgram/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.

Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving 1α-OHD3 in a dose of 0.5- 1.0 microgram/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

5.2 Pharmacokinetic properties

Alfacalcidol is absorbed passively and almost completely in the small intestine.

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

The half-life of alfacalcidol is about 4 hours. The pharmacologic effect is 3-5 days.

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.

5.3 Preclinical safety data

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

Genotoxicity:
Alfacalcidol is not genotoxic.

Reproduction toxicity:
No specific effects of alfacalcidol on fertility or behaviour of the offspring were noted in rats and rabbits. In terms of embryo-fetal development, fetal 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

Citric Acid, Anhydrous
all-rac-α-Tocopherol
propyl gallate,
Ethanol, Anhydrous
Arachis Oil, Hydrogenated

The capsule shell contains:
gelatin glycerol
anidrisorb
Purified Water
Medium Chain Triglyceride

The capsules contain the following colours:
1.0 microgram capsules: titanium dioxide (E171) and ferric oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

The finished products are Alfacalcidol 1.0 mcg capsules soft, to be marketed in white opaque HDPE container, with white opaque HDPE screw closure and induction sealing.

HDPE Container pack: Pack size: 30 capsules, 50 capsules and 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Arcolab International Limited
Unit 4, Metro Centre
Tolpits Lane
Watford, Hertfordshire
WD 189 SS UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 28176/0158

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2014

10 DATE OF REVISION OF THE TEXT

18/09/2015