SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol Aristo 0.25 microgram Capsules, soft
Alfacalcidol Aristo 0.5 microgram Capsules, soft
Alfacalcidol Aristo 1.0 microgram Capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol Aristo 0.25 microgram capsule, soft: Each soft capsule contains 0.25 microgram alfacalcidol
Alfacalcidol Aristo 0.5 microgram capsule, soft: Each soft capsule contains 0.5 microgram alfacalcidol
Alfacalcidol Aristo 1.0 microgram capsule, soft: Each soft capsule contains 1.0 microgram alfacalcidol

Excipient:
Alfacalcidol Aristo 0.25 microgram capsule, soft: Each soft capsule contains:
98.7 mg Arachis oil (peanut oil)

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

Alfacalcidol Aristo 1.0 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 Aristo 0.25 mcg Capsule, soft (capsule): Reddish brown colored, oval shaped soft gelatin capsules containing clear oily liquid. The size is approximately 10.4 mm X 5.6 mm

Alfacalcidol Aristo 0.5 mcg Capsule, soft (capsule): Light pink colored, oval shaped soft gelatin capsules containing clear oily liquid. The size is approximately 10.4 mm X 5.6 mm

Alfacalcidol Aristo 1.0 mcg Capsule, soft (capsule): Pale yellow colored, oval shaped soft gelatin capsules containing clear oily liquid. The size is approximately 10.4 mm X 5.6 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfacalcidol Aristo 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) Nutritional and malabsorptive rickets and osteomalacia
e) Pseudo-deficiency (D-dependent) rickets and osteomalacia
f) Hypophosphataemic vitamin D resistant rickets and osteomalacia

4.2 Posology and method of administration

Adults and paediatric patients over 20 kg bodyweight: 1 microgram/day
Elderly patients: 0.5 microgram/day
Paediatric patients under 20 kg bodyweight: 0.05 microgram/kg/day

The dose of alfacalcidol should be adjusted based on bi-weekly measurements of plasma concentrations of calcium and phosphorous. The daily dose of alfacalcidol capsules may be increased by increments of 0.25 - 0.5 microgram. When the dosage is established, plasma levels of calcium, phosphorous and creatinine should be taken every 2-4 weeks.

Most adult patients respond to doses between 1 and 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 Aristo should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

Method of administration: Oral

The capsules should be swallowed preferably with a drink of water. The capsules must not be chewed or crushed.

Paediatric population.
The capsule must not be chewed or crushed. Small children may not be able to swallow the capsule and an alternative administration form, e.g. oral drops, should be considered.

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). PTH, alkaline phosphatase and the calcium x phosphate product should be monitored if considered clinically indicated. Hypercalcaemia may appear in patients treated with Alfacalcidol Aristo. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. Signs of hypercalcaemia are:

- anorexia
- constipation or diarrhoea
- polyuria
- polydipsia
- sweating
- weakness, headache, nausea, dry mouth
- muscle and bone pain
- metallic taste
- somnolence
- vertigo

Hypercalcaemia may quickly be corrected for by discontinuing alfacalcidol treatment in about one week until the calcium level has normalized. Alfacalcidol may then be restarted at a reduced dose (at half the last dose used) and continued monitoring of plasma calcium**.**
In rare cases, severe hypercalcaemia may appear. This condition is potential life threatening and require acute, active treatment, see section 4.9.

Prolonged hypercalcemia can aggravate atherosclerosis, heart valve sclerosis and nephrolithiasis. When alfacalcidol is used in patients with these diseases, prolonged hypercalcemia should be avoided. Transient and also prolonged deterioration of renal function is observed. Alfacalcidol should be used with caution in patients with calcifications in the lungs, as this can result in heart disease.

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.

Alfacalcidol should be used with caution in patients with granulomatous diseases such as sarcoidosis, where the sensitivity of vitamin D is increased due to increased hydroxylation activity.

In hypercalcaemia due to vitamin D administration the risk of cardiac arrhythmias is increases with concomitant use of digitalis glycosides.

During treatment with Alfacalcidol Aristo serum calcium and serum phosphate should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses.

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

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.

Vitamin D containing preparations/Other Vitamin D analogues

Concurrent use of vitamin D containing preparations with alfacalcidol may enhance the risk of hypercalcaemia. Use of multiple vitamin D analogues should also 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 Alfacalcidol Aristo.

Magnesium-containing antacids

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

Aluminium-containing preparations

Alfacalcidol Aristo 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 alfacalcidol formulations. Alfacalcidol Aristo 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.

Digitalis preparations

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias.

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).
Alfacalcidol should not be used during pregnancy unless clearly necessary as hypercalcaemia during pregnancy may cause congenital malformations. Caution should be taken in fertile women.

Breast-feeding:
Alfacalcidol is excreted in human milk. It must be decided whether to discontinue breastfeeding or to discontinue/avoid treatment with alfacalcidol, taking into account the child´s benefit of breast-feeding and the woman´s benefit of treatment.

Breast-fed infants of alfacalcidol-using mothers should be monitored closely for hypercalcaemia.

Fertility
There are no clinical studies on the effect of alfacalcidol on fertility. A pre-clinical study did not show an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Alfacalcidol Aristo has no or negligible influence on the ability to drive or use machines. The patient should be informed that dizziness may occur during treatment and take the necessary precautions while driving or using machines.

4.8 Undesirable effects

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

Symptoms of hypercalcaemia are headache, weakness, hypertension, somnolence, dizziness, sweating, anorexia, nausea, vomiting, diarrhoea, constipation, polyuria, polydipsia and muscle and bone pain, and metallic taste.

Prolonged hypercalcemia can lead to nefrokalcinose/nephrolithiasis and reduced kidney function, see section. 4.4. 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 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 reactions such as erythematous, maculo-papular 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 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 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 Appendix V*.

4.9 Overdose
Hypercalcaemia is treated by suspending the administration of Alfacalcidol Aristo.

For a description of symptoms of hypercalcaemia see section 4.8. In severe cases of hypercalcaemia general supportive measures should be undertaken. Keep the patient well hydrated by i.v. infusion of saline (forced 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

Mechanism of action
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.

Clinical efficacy and safety

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

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

Biotransformation and elimination
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 Aristo and 1,25-dihydroxyvitamin D are very similar. 1,25-dihydroxyvitamin D is transported in the blood by a specific transport protein (a globulin). Vitamin D is metabolised to several polar inactive metabolites and is excreted primarily through the bile.

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

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

The capsules contain the following colours:
0.25 microgram capsules: titanium dioxide (E171), ferric oxide red (E172) & ferric oxide black (E172)
0.5 microgram capsules: titanium dioxide (E171) and ferric oxide red (E172)
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 0.25 mcg, 0.5 mcg and 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 and 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH, Wallenroder Straße 8-10, 13435 Berlin, Germany

8 MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10 DATE OF REVISION OF THE TEXT

<To be completed nationally>