SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alfacalcidol Crinex 0,25 microgram, zachte capsules
Alfacalcidol Crinex 0,5 microgram, zachte capsules
Alfacalcidol Crinex 1 microgram, zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol Crinex 0.25 microgram soft capsule: Each soft capsule contains 0.25 microgram alfacalcidol
Alfacalcidol Crinex 0.5 microgram soft capsule: Each soft capsule contains 0.5 microgram alfacalcidol
Alfacalcidol Crinex 1.0 microgram soft capsule: Each soft capsule contains 1.0 microgram alfacalcidol

Excipient(s) with known effect

Each soft capsule contains 22 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft
Alfacalcidol Crinex 0.25 microgram: Clear colourless, oily liquid fill in oval, white, opaque soft gelatin capsule. The size is approximately 9.7 mm X 6.8 mm
Alfacalcidol Crinex 0.5 microgram: Clear colourless, oily liquid filled in oval, red, opaque soft gelatin shell capsule. The size is approximately 9.7 mm X 6.8 mm
Alfacalcidol Crinex 1.0 microgram: Clear colourless, oily liquid fill in oval, brown, opaque soft shell gelatin capsule. The size is approximately 9.7 mm X 6.8 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Severe or progressive secondary hyperparathyroidism in patients with moderate to severe chronic renal impairment, including those under dialysis
- Hypoparathyroidism
- Pseudo-deficiency (D-dependent) rickets and osteomalacia
- Hypophosphataemic vitamin D resistant rickets and osteomalacia

Alfacalcidol is indicated in children above 4 years, adolescents and adults.

4.2 Posology and method of administration

Posology

The optimal daily dose must be determined individually by the treating doctor on the basis of the serum calcium level. Treatment must always be started at the lowest possible dose.

Adults
Dosing recommendations for all indications: 0.25-0.50 microgram/day.

The dose of alfacalcidol should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response (i.e. calcium, phosphate and PTH).

The daily dose of alfacalcidol may be increased by increments of 0.25 - 0.5 microgram.

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.

Other formulations are available in case a dosage less than 0.25 micrograms need to be administered.

Severe or progressive secondary hyperparathyroidism in patients with moderate to severe chronic renal impairment:
Before and during treatment with alfacalcidol , 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.

In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, pre-operative treatment with alfacalcidol for 2-3 weeks does not aggravate 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.

Hypoparathyroidism:
Severe hypocalcaemia is corrected more rapidly with higher doses of alfacalcidol (e.g., 3-5 micrograms) together with calcium supplements.

Pseudo-deficiency (D-dependent) rickets and osteomalacia:
For treatment 0.5 to 2.0µg is advised. Alfacalcidol should be part of a treatment including vit D, 25(OH) vit D and 1α(OH) vit D

Hypophosphataemic vitamin D-resistant rickets and osteomalacia:
Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with alfacalcidol (1 to 3 µg/day) rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

Renal impairment
Therapy is most beneficial in patients with low plasma calcium, elevated PTH and alkaline phosphatase, and evidence of renal bone disease.

Hepatic impairment
The efficacy of alfacalcidol is generally maintained in patients with hepatic impairment. In patients with severe hepatic impairment, the effect of alfacalcidol may be reduced due to decreased hydroxylation of alfacalcidol to calcitriol, or reduced absorption which may necessitate a higher dose (see section 5.2).

Paediatric population (>4 years)
Dosing recommendations for all indications: 0.25-0.50 microgram/day.

Other formulations are available in case a dosage less than 0.25 micrograms needs to be administered for children younger than 4 years or in case children are unable to swallow capsules.

Method of administration

Oral.

4.3 Contraindications

Hypercalcaemia.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Monitoring
During treatment with alfacalcidol serum calcium, serum phosphate levels and creatine, levels should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses.
PTH, alkaline phosphatase and the calcium x phosphate product should be monitored if considered clinically indicated.

Alfacalcidol should be used with caution for:

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

Hypercalcaemia
Hypercalcaemia may appear in patients treated with alfacalcidol. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia (see section 4.9).

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.

Treatment with phosphate binders concomitantly with alfacalcidol may be considered to avoid the risk of increased serum phosphate and possible calcifications.

Alfacalcidol should be used with caution in patients with granulomatous diseases, such as sarcoidosis, in which sensitivity to vitamin D increases due to increased hydroxylation activity.

This medicine contains 22 mg sorbitol in each dosage unit. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac glycosides including digitalis
Hypercalcaemia in patients taking cardiac glycosides may precipitate cardiac arrhythmias.

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

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

Thiazide diuretics and calcium-containing preparations
Concurrent administration of thiazide diuretics or calcium-containing preparations may increase the risk of hypercalcemia. Calcium levels should be monitored.

Magnesium based antacids and laxatives
Magnesium based antacids and laxatives should not be used during treatment with alfacalcidol due to increased risk of hypermagnesaemia.

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.

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

Fertility
No fertility data is available for use of alfacalcidol.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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.

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 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*
	Hyperphosphatemia
Nervous system disorders	
Uncommon:	*Headache*
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.*
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*

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 Nederlands Bijwerkingen Centrum Lareb.
Website: www.lareb.nl.

4.9 Overdose

Hypercalcaemia is treated by suspending the administration of Alfacalcidol Crinex.

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: Vitamins; Vitamin D and analogues. ATC code: A11CC03.

Mechanism of action
Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxyvitamin D3, the Vitamin D3 metabolite which acts as a regulator of calcium and phosphate metabolism. Due to this rapid conversion, the therapeutic benefits of alpha D3 (alfacalcidol) are virtually the same as those of 1,25-dihydroxyvitamin D3. The main effects are to increase circulating 1,25- dihydroxyvitamin D3 levels, and thereby to increase intestinal absorption of calcium and phosphate, promote bone mineralisation, decrease plasma parathyroid hormone levels as well as to decrease bone resorption, with relief of bone and muscle pain.

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, 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 Crinex.

Pharmacodynamic effects
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 Crinex 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

Absorption
Alfacalcidol is absorbed passively and almost completely in the small intestine. Serum levels of 1,25 dihydroxyvitamin D3 reach peak concentrations approximately 8-12 hours after a single dose of alfacalcidol with a half-life of 1,25-(OH)2 -D3 of about 35 hours. The metabolism is similar to that of vitamin D after the 25-hydroxylation to 1,25 dihydroxyvitamin D3.

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.

Biotransformation
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 Crinex and 1,25-dihydroxyvitamin D are very similar.

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

Specific populations
Renal impairment
Patients with chronic kidney disease exhibit decreased conversion of 25-hydroxyvitamin D_3 (25-OHD3) to its active form, calcitriol (1,25-OH2D3), due to impaired renal 1α-hydroxylase activity. Alfacalcidol is a 1α-OHD3 analog, which is converted to calcitriol in the liver. It is used to bypass the impaired renal hydroxylation in patients with reduced renal function.

Hepatic impairment
Alfacalcidol, is a prodrug requiring 25-hydroxylation in the liver to become metabolically active as calcitriol. Hepatic impairment rarely limits the conversion of alfacalcidol to calcitriol, but severe liver disease may compromise its metabolism and 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

The capsule fill contains:
Butylated hydroxyanisole (E320)
Butylated hydroxytoluene (E320)
Triglycerides, medium-chain
The capsule shell contains:
Gelatin (E441)
Glycerol (E422)
Sorbitol Liquid (non-crystallising (E420)

0.25 microgram capsules:
Titanium dioxide (E171)

0.5 microgram capsules:
Titanium dioxide (E171)
Allura red AC (E129)
Brilliant blue FCF (E133)
Iron oxide, yellow (E172)

1 microgram capsules:
Iron oxide, black (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC Film/Aluminium blisters packs containing 30, 60, 90 or 120 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRES CRINEX
1 B Rue Rene Anjolvy
94250 Gentilly
Frankrijk

8. MARKETING AUTHORISATION NUMBER(S)

Alfacalcidol Crinex 0,25 microgram, zachte capsules - RVG 134933
Alfacalcidol Crinex 0,5 microgram, zachte capsules - RVG 134936
Alfacalcidol Crinex 1 microgram, zachte capsules - RVG 134937

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 28 juli 2026

10. DATE OF REVISION OF THE TEXT