

**ALFACALCIDOL 0.25 MICROGRAMS CAPSULES
PL 19053/0010**

**ALFACALCIDOL 0.5 MICROGRAMS CAPSULES
PL 19053/0011**

**ALFACALCIDOL 1 MICROGRAMS CAPSULES
PL 19053/0012**

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PL 19053/0011**

**ALFACALCIDOL 1 MICROGRAMS CAPSULES
PL 19053/0012**

LAY SUMMARY

The Medicines Healthcare and products Regulatory Agency granted Tenlec Pharma Limited Marketing Authorisations (licences) for the medicinal products Alfacalcidol 0.25 microgram Capsules (PL 19053/0010), Alfacalcidol 0.5 microgram Capsules (PL 19053/0011) and Alfacalcidol 1.0 microgram Capsules (PL 19053/0012). These are prescription only medicines (POM). Alfacalcidol is a vitamin D product. Vitamin D is used in the processes which look after the growth of bones and helps to keep them healthy. Calcium and phosphate are also needed to help bones grow and keep them healthy. Alfacalcidol also helps calcium and phosphate to be absorbed more effectively from the intestines.

Alfacalcidol is used to treat renal (kidney) bone diseases as well as rickets, osteomalacia (which is a disease causing the bones to soften and weaken) and patients with high or low activity of the parathyroid gland. It is used to maintain normal calcium levels within the body.

Alfacalcidol 0.25 microgram Capsules, Alfacalcidol 0.5 microgram Capsules and Alfacalcidol 1.0 microgram Capsules were considered the same as the original products One-Alpha Capsules 0.25, 0.5 and 1 microgram marketed by Leo Laboratories Ltd, (PL 00043/0052/0206/0050). No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Alfacalcidol 0.25 microgram Capsules, Alfacalcidol 0.5 microgram Capsules and Alfacalcidol 1.0 microgram Capsules outweigh the risks; hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Alfacalcidol 0.25 microgram Capsules, Alfacalcidol 0.5 microgram Capsules and Alfacalcidol 1.0 microgram Capsules on 28th October 2009. The products are prescription only medicines.

These are three strengths of Alfacalcidol submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, and have been shown to be generic medicinal products of the original products One-Alpha Capsules 0.25, 0.5 and 1 microgram marketed by Leo Laboratories Ltd, (PL 00043/0052, PL 00043/0206 & PL 00043/0050).

The products contain the active ingredient alfacalcidol, which is a vitamin D product used for treating conditions in which calcium metabolism is disturbed due to impaired 1 α -hydroxylation and other disorders associated with vitamin D resistance. The medicine is used to treat vitamin D deficiency in people who have certain types of metabolic problems. This may include people who have: kidney problems; low levels of calcium or phosphate in the blood; problems with their parathyroid gland; rickets or osteomalacia.

These applications for Alfacalcidol 0.25 mcg, 0.5 mcg and 1 mcg Capsules were submitted at the same time and depend on disintegration studies; comparing the applicant's products with the reference products One-Alpha Capsules 0.25, 0.5 and 1 mcg marketed by Leo Laboratories Ltd as well as a bioequivalence study; comparing Teva AlfaD 0.25mcg, 0.5 mcg & 1 mcg capsules (which have the same product composition as the applicant's products) with the Leo reference products. Consequently, all sections of this Scientific Discussion refer to all three products.

The applications for Alfacalcidol 0.25, 0.5 and 1 microgram Capsules are made on the basis that the proposed products are generic medicinal products of One-Alpha Capsules 0.25, 0.5 and 1 microgram marketed by Leo Laboratories Ltd, (PL 00043/0052/0206/0050).

PHARMACEUTICAL ASSESSMENT

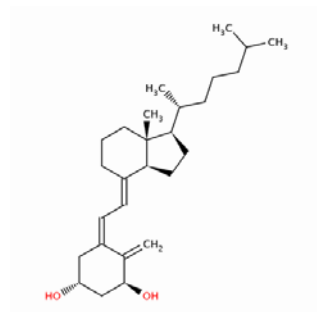
DRUG SUBSTANCE

Alfacalcidol

INN: Alfacalcidol

Chemical name: 1- α -hydroxycholecalciferol; (1 α ,3 β ,5Z,7E)-Secocholesta-5,7,10(19)-triene-1,3-diol

Structural Formula:



Molecular formula: $C_{27}H_{44}O_2$

Molecular weight: 400.6.g/mol

Physical form: White or almost white crystals.

Solubility: practically insoluble in water, freely soluble in alcohol, soluble in fatty oils.

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer.

An appropriate specification is provided for the active substance alfacalcidol.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

An impurity profile for the drug substance has been provided and the impurities described are identical to those in the European Pharmacopoeial monograph for alfacalcidol.

Active alfacalcidol is stored in appropriate packaging material. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

An adequate retest period has been defined based on conducted stability studies.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely anhydrous citric acid, propyl gallate, alpha-tocopherol, anhydrous ethanol and arachis oil. All the ingredients within the capsule comply with their relevant Ph Eur monograph.

The capsule shell contains: gelatin, glycerol, sorbitol and red iron oxide (0.25microgram capsule), red iron oxide and titanium dioxide (0.5microgram capsule), yellow iron oxide and titanium dioxide (1microgram capsule) and the printing ink contains; shellac, black iron oxide and propylene glycol. All the ingredients within the shell and printing ink comply with their relevant monographs with the exception of black iron oxide which in the absence of Ph Eur monograph is controlled by the Japanese Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. The only excipient that contains material of animal or human origin is gelatin. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

Development Pharmaceutics

The aim of the development process was to obtain capsules essentially similar to the brand leader products (One-Alpha Capsules – Leo).

Disintegration profiles

The disintegration time of one batch each of the applicant's capsules have been compared with 2 batches each of the reference products (Leo, UK). Disintegration times are comparable with that of the reference products

Essential Similarity/Bioequivalence

No bioequivalence data has been submitted with this application.

The applicant's products are essentially similar in having the same qualitative and quantitative composition of active ingredient and the same pharmaceutical form as the Teva products (AlfaD Capsules- PL 00289/0459-0461).

Bioequivalence of Teva's product versus the brand leader's product has been demonstrated (please see the clinical section of this report) and the only difference between the Teva product and this application is with the capsule shell. Bioequivalence can be assumed as disintegration times of the Teva products and current applications are similar. The active substance is dissolved in an oily base and filled into soft gelatin capsules. The bulk solutions used to fill capsules are the same as that used in the Teva products (AlfaD Capsules- PL 00289/0459-0461).

The ratio between active substance and excipients are not the same and conditions for exemption from additional bioequivalence studies for other strengths are not strictly met. However since the drug is lipid soluble the latter requirements is not applicable as drugs may be absorbed by fat absorption pathways and differences in ratio of active to excipients is not a critical factor influencing absorption. As the disintegration times of the test product and the reference product (Leo products) are similar it can be

concluded that the differences in capsules shell do not affect the bioavailability and that the test product is a generic medicinal product of the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is presented in a blister composed of aluminium strips with 10 capsules, in packs of 30 capsules. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. The precaution 'Do not store above 25°C', 'Store in the original package' and 'Keep blister in the outer carton' has been included.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION & BACKGROUND

Alfacalcidol is used for treatment of conditions in which calcium metabolism is disturbed due to impaired 1 alpha-hydroxylation and other disorders associated with Vitamin D resistance.

Alfacalcidol has been used clinically for approximately thirty years, and was initially approved for marketing in the UK in 1978. It is currently listed in the British National Formulary.

Approval for the Alfacalcidol Biogal Capsules are therefore sought on the basis that they are essentially similar to the Leo One Alpha products that have already demonstrated efficacy and safety.

2. INDICATIONS

The proposed indications have been compared with the indications approved for the current UK Teva MAs for alfacalcidol, AlfaD capsules, PLs 00289/0459/0460/0461, granted 25/01/2002.

Assessor's comment

Satisfactory

3. POSOLOGY AND METHOD OF ADMINISTRATION

The proposed Posology and Method of Administration have been compared with the Posology and Method of Administration approved for the current UK Teva MAs for alfacalcidol, AlfaD capsules, PLs 00289/0459/0460/0461, granted 25/01/2002.

Assessor's comment

Satisfactory

4. TOXICOLOGY

Not assessed.

5. CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Not assessed.

BIOAVAILABILITY

Approval for the proposed products is being requested on the basis that they are generic medicinal products of the Leo Laboratories One Alpha products.

No clinical pharmacokinetic study has been submitted to support "essential similarity" between the proposed products and the Leo Laboratories One Alpha products. However, the active ingredient used in the applicant's products is identical to that used by Teva for their alfacalcidol products, which have been established as generic medicinal products of Leo's One Alpha capsules. Therefore, it is reasonable to

assume that there will be “essentially similar” quantitative and qualitative impurity profiles for the Tenlec, Teva and Leo products.

The bioequivalence data given below compares the reference products with the Teva products.

Pharmacokinetics- bioequivalence study Teva

A randomised two-way crossover bioavailability study was carried out in healthy male volunteers comparing a single dose of 1mcg of the product versus the market leader One Alpha Capsules. Calcitriol levels were determined before dosing and regularly for up to 72 hours post-dosing and there was a wash-out interval of 14 days between treatment periods.

Statistical analysis included ANOVA, non-parametric 95% confidence interval and two one-sided test (90% confidence interval).

	Reference (A) Mean s.d	Test (B) Mean s.d	Ratio B/A	Classical 95% confidence interval
AUC 48h (pg.h/ml)	1735.58	1780.95	1.026	95.2-110.1
AUC 72h (pg.h/ml)	2206.20	2271.45	1.030	96.7-109.3
Cmax (pg/ml)	60.51	61.57	1.017	93.4-110.1

	ANOVA		Non-parametric 95% confidence interval	Two one-sided test 90% confidence interval
	EMS	Power at alpha=0.05		
AUC48h	28978.2	1.000	95.4-105.3	96.5-108.7
AUC 72h	33601.4	1.000	95.7-107.6	97.8-108.1
Cmax	43.93	0.998	93.5-107.8	94.9-108.6

A= reference product: single oral dose of four One-Alpha 1.-microgram capsules (Leo Laboratories Ltd., UK)

B= Test product: Single oral dose of four Alfacalcidol 1.0microgram capsules (Teva Pharmaceutical Industries Ltd., Israel).

Conclusion:

The comparative bioavailability study of alfacalcidol in healthy male volunteers demonstrates bioequivalence of One-Alpha 1.0 microgram capsules manufactured by Leo Laboratories Ltd., and Alfacalcidol 1.0 microgram capsules manufactured by Teva Pharmaceutical Industries Ltd.

The Company have included the following justification for “essential similarity” with respect to the clinical safety and efficacy of the proposed products in the Clinical Expert Report.

Company Justification

The same product composition (qualitative and quantitative with respect to the active ingredient) is used for both the proposed products and the Leo products. (The composition of the three different strengths of Alfacalcidol 0.25, 0.5 & 1mcg Capsules is virtually identical.

The Leo and applicant’s products are formulated as an oily solution within a soft gelatin capsule. This effectively means that delivery to the patient is as an oral solution. Thus, the disintegration time for the gelatin capsules is critical. The capsules do disintegrate rapidly. The rate being similar to that for One Alpha products (Leo Laboratories) and this is within pharmacopoeial limits.

In a study performed by the applicant, the disintegration times of all three capsule strengths of the test product and reference Leo product were recorded. The results showed similar disintegration times. Thus, Alfacalcidol 0.25, 0.5 & 1mcg capsules are considered equivalent to the Leo reference product.

Bioavailability of the dosage form

No clinical pharmacology studies are submitted for Alfacalcidol 0.25, 0.5 & 1 mcg Capsules. This is considered justified because the formulation is as an oily solution within a soft gelatin capsule.

The capsules are known to rapidly disintegrate and thus the active ingredient will be effectively presented in the stomach as an immediately available oral solution. Furthermore, as the disintegration rate of the capsules is comparable with that of Leo One Alpha capsules, essential similarity with respect to bioavailability can be claimed.

This is in accordance with the conditions set out in the ‘Note for Guidance on The Investigation of Bioavailability and Bioequivalence’ (CPMP/EWP/QWP/140/98). Therefore, additional bioequivalence testing is considered unnecessary.

6. EFFICACY

Not assessed. No efficacy trials with the proposed products were submitted.

The Company state that as the products are essentially similar to products existing on the UK market, under the derogation allowed by Article 10.1(a)(iii) of Directive 2001/83/EC, no additional studies are submitted with these applications.

Assessor’s comment

Satisfactory.

7. SAFETY

No new or unexpected safety concerns are considered to arise from the use of the proposed products.

Assessor’s comment

Satisfactory.

8. EXPERT REPORT

A Clinical Expert Report has been written by a suitably qualified person.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The Summaries of Product Characteristics (SmPC) for all three products are satisfactory.

10. PATIENT INFORMATION LEAFLET

The patient information leaflets for all three products are satisfactory.

11. LABELLING

The labelling for all three products is satisfactory.

12. DISCUSSION

The grant of these Marketing Authorisations is recommended for these three formulations of alfacalcidol.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Alfacalcidol 0.25mcg, 0.5mcg & 1mcg Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between Teva AlfaD 0.25mcg, 0.5 mcg & 1mcg capsules (which have the same product composition as the applicant's products) and the reference products One-Alpha Capsules 0.25, 0.5 and 1 mcg marketed by Leo Laboratories Ltd. Disintegration studies have also been carried out comparing the applicant's products with the reference products One-Alpha Capsules 0.25, 0.5 and 1mcg.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with alfacalcidol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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**ALFACALCIDOL 0.5 MICROGRAMS CAPSULES
PL 19053/0011**

**ALFACALCIDOL 1 MICROGRAMS CAPSULES
PL 19053/0012**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 28 th January 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 12 th March 2003.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 11 th December 2006, 13 th February 2009.
4	The applicant responded to the MHRA's requests, providing further information on 11 th August 2008 and 8 th June 2009 for the quality sections.
5	The applications were determined on 28 th October September 2009.

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PL 19053/0012**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 0.25 Microgram Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains 0.25 microgram of alfacalcidol.

Each soft gelatin capsule also contains 98.8mg of Arachis oil (refined), 1.15mg ethanol and 4.53mg of sorbitol 70%

For full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Oval, opaque reddish brown, elastic, soft gelatin capsule printed with "0.25" containing a clear, pale yellow, oily solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alfacalcidol is used for treating conditions in which calcium metabolism is disturbed due to impaired 1 α -hydroxylation and other disorders associated with Vitamin D resistance.

The main indications are:

- Renal osteodystrophy
- Hypoparathyroidism
- Hyperparathyroidism (with bone disease)
- Nutritional and malabsorptive rickets and osteomalacia
- Hypophosphataemic Vitamin-D resistant rickets and osteomalacia
- Pseudo-deficiency (D-dependent Type 1) rickets and osteomalacia

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

All indications -

Starting dose:

Children 20 kg and over:	1 microgram/day
Adults:	1 microgram/day
Elderly patients:	0.5 microgram/day

The dose should subsequently be adjusted according to the biochemical response to avoid hypercalcaemia. Plasma calcium levels (preferably corrected for protein binding) should initially be measured weekly. The dose of Alfacalcidol can be increased by increments of 0.25 to 0.5 micrograms/day. Most adults respond to doses of 1 to 3 micrograms/day. Once the dose is stabilised, calcium levels may be measured every 2-4 weeks.

Indices of response, in addition to plasma calcium, may include alkaline phosphatase, parathyroid hormone levels, bone radiography and histological investigations. When there is biochemical or radiographic evidence of bone healing (or in hypoparathyroidism when calcium levels have normalised) the dose required for maintenance generally decreases to around 0.25 to 1 microgram/day. Should hypercalcaemia occur, Alfacalcidol should be stopped until plasma calcium returns to normal (usually about a week), and then restarted at one half of the previous dose.

Renal Osteodystrophy - Patients with already high plasma calcium levels may have autonomous hyperparathyroidism. In this situation they may not respond to alfacalcidol and other therapeutic measures may be indicated.

In patients with chronic renal disease it is particularly important to check the plasma calcium frequently because prolonged hypercalcaemia may further impair renal function.

Before and during Alfacalcidol treatment, the use of phosphate binding agents to prevent hyperphosphataemia may also be considered.

Hypoparathyroidism - Low plasma calcium levels may be restored to normal more quickly with Alfacalcidol than with parent Vitamin D. Severe hypocalcaemia is corrected more

rapidly with higher doses of Alfacalcidol (e.g. 3-5 micrograms) together with calcium supplements.

Hyperparathyroidism - In patients needing surgery for primary or tertiary hyperparathyroidism, pre-operative treatment with Alfacalcidol for 2-3 weeks can reduce bone pain and myopathy without aggravating hypercalcaemia. To decrease the risk of post-operative hypocalcaemia, Alfacalcidol should be continued until the plasma alkaline phosphatase falls to normal or hypercalcaemia occurs.

Nutritional and Malabsorptive Rickets and Osteomalacia - Malabsorptive osteomalacia, which responds to large doses of intramuscular or intravenous parent Vitamin D, will respond to small oral doses of AlfaD. Nutritional rickets and osteomalacia can also be rapidly corrected with AlfaD.

Hypophosphataemic Vitamin D-Resistant Rickets and Osteomalacia - Normal doses of Alfacalcidol rapidly relieve myopathy when present, and increase calcium and phosphate retention. Phosphate supplements may also be required in some patients. Neither large doses of parent Vitamin D nor phosphate supplements are entirely satisfactory in these conditions.

Pseudo-Deficiency (D-Dependent Type1) Rickets and Osteomalacia - As with the nutritional conditions, similar oral doses of Alfacalcidol are effective in circumstances which would require high doses of parent Vitamin D.

Use in Children

Alfacalcidol Capsules are not indicated in children under 20 kg as the dosage cannot be titrated adequately.

Use in Elderly

Initiation of therapy requires a lower dose in elderly patients. The clinical manifestations of hypo- or hypercalcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

4.3 CONTRAINDICATIONS

Alfacalcidol should not be used by patients with evidence of Vitamin D toxicity or known hypersensitivity to the effects of Vitamin D or any of its analogues. Alfacalcidol Capsules contain arachis oil (peanut oil) and should not be used by patients with peanut allergy. As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid Alfacalcidol Capsules.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Alfacalcidol increases the internal absorption of calcium and phosphate, serum levels of which should be monitored, particularly in patients with renal failure.

If hypercalcaemia or hypercalciuria occur this can be corrected rapidly by stopping treatment with Alfacalcidol and any calcium supplements until plasma calcium levels return to normal, usually in about a week. Alfacalcidol may then be restarted at half the last dose used.

Response to alfacalcidol may be impaired if the diet is markedly deficient in calcium.

Healing of bone lesions often indicates a decreased requirement for Alfacalcidol in which case appropriate dose adjustments should be made (see Posology and Method of Administration).

Alfacalcidol Capsules contain small amounts of ethanol (alcohol), approximately 1mg per capsule.

The capsule shell contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol may cause gastro-intestinal disturbance.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias. Patients taking digitalis concurrently with alfacalcidol must therefore be closely monitored.

Patients on barbiturates or other anticonvulsants may require an increased dose of Alfacalcidol to produce the desired effect.

Absorption of alfacalcidol may be impaired by concurrent use of mineral oil (prolonged use), colestyramine, colestipol, sucralfate or large amounts of aluminium-based antacids.

Caution should be exercised in the use of magnesium-based antacids or laxatives for patients taking alfacalcidol who are on chronic renal dialysis. Hypermagnesaemia may occur.

The risk of hypercalcaemia is increased in patients taking calcium-containing preparations or thiazide diuretics concurrently with alfacalcidol.

Alfacalcidol is a potent derivative of Vitamin D. Pharmacological doses of Vitamin D or its analogues should not be given during alfacalcidol treatment because of the possibility of additive effects and an increased risk of hypercalcaemia.

4.6 PREGNANCY AND LACTATION

There is insufficient evidence on which to assess the safety of alfacalcidol use during pregnancy, although it has been widely used for many years without apparent adverse effects. Animal studies have not revealed any hazard but as with all drugs, Alfacalcidol should only be used during pregnancy if treatment is essential and no better alternative is available.

Although not definitely established, it is likely that increased levels of 1,25-dihydroxyvitamin D₃ will be found in the breast milk of mothers treated with alfacalcidol. This might have an influence on calcium metabolism in a breast-fed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Adverse effects generally relate to abnormally elevated serum calcium levels leading to symptoms of anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised plasma and urine concentrations of calcium and phosphate.

In the case of renal impairment, elevated serum phosphate levels may be induced by Alfacalcidol therapy. The dosage should be adjusted to the patient's requirements.

4.9 OVERDOSE

Excessive intake of vitamin D leads to the development of hypercalcaemia. Administration of Alfacalcidol should be stopped if hypercalcaemia occurs symptoms of which include anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised plasma and urine concentrations of calcium and phosphate. Severe hypercalcaemia may require treatment with general supportive measures, with intravenous fluids, with a loop diuretic or with corticosteroids.

In acute overdosage, early treatment with gastric lavage and/or the administration of mineral oil may reduce absorption and promote faecal elimination.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

ATC Code: A11C C03 (Vitamin A and D, incl. combinations of the two, vitamin D and analogues).

When 1- α -hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D₃ production is reduced. Disorders in which this can occur include renal bone disease, hypoparathyroidism and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their correction but will respond to small doses of Alfacalcidol, which does not depend on the renal 1- α -hydroxylation process.

When using parent Vitamin D, the high dose and variable response time can lead to unpredictable hypercalcaemia which may take many weeks, sometimes months, to reverse. With Alfacalcidol, the more rapid onset of response allows better titration of dose and, if hypercalcaemia does occur, it can be reversed within days of stopping treatment.

5.2 PHARMACOKINETIC PROPERTIES

Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxy-vitamin D₃, the Vitamin D₃ metabolite which acts as a regulator of calcium and phosphate metabolism.

5.3 PRECLINICAL SAFETY DATA

There are no pre-clinical data of relevance to the prescriber, which are additional to that provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule Contents

Citric Acid, Anhydrous (E330)
Propyl Gallate (E310)
 α -Tocopherol (E307)
Ethanol, Anhydrous
Arachis Oil (peanut oil)

Soft Gelatin Capsule Shell

Gelatin
Glycerol
Sorbitol
Red iron oxide (E172)

Printing Ink

Shellac
Black iron oxide
Propylene glycol

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

Cold form aluminium-aluminium blister strips each with 10 capsules, in packs of 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

- 7 MARKETING AUTHORISATION HOLDER**
Tenlec Pharma Ltd.
Hailsham,
East Sussex BN27 1PQ
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 19053/0010
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
28/10/2009
- 10 DATE OF REVISION OF THE TEXT**
28/10/2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 0.5 microgram Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains 0.5 microgram of alfacalcidol.

Each soft gelatin capsule also contains 98.8mg of Arachis oil (refined), 1.15mg ethanol and 4.53mg of sorbitol 70%.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Oval, opaque pale pink, elastic soft gelatin capsule printed with "0.5" containing clear, pale yellow, oily solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alfacalcidol is used for treating conditions in which calcium metabolism is disturbed due to impaired 1α -hydroxylation and other disorders associated with Vitamin D resistance.

The main indications are:

- Renal osteodystrophy
- Hypoparathyroidism
- Hyperparathyroidism (with bone disease)
- Nutritional and malabsorptive rickets and osteomalacia
- Hypophosphataemic Vitamin-D resistant rickets and osteomalacia
- Pseudo-deficiency (D-dependent Type 1) rickets and osteomalacia

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

All indications -

Starting dose:	Children 20 kg and over:	1 microgram/day
	Adults:	1 microgram/day
	Elderly patients:	0.5 microgram/day

The dose should subsequently be adjusted according to the biochemical response to avoid hypercalcaemia. Plasma calcium levels (preferably corrected for protein binding) should initially be measured weekly. The dose of Alfacalcidol can be increased by increments of 0.25 to 0.5 micrograms/day. Most adults respond to doses of 1 to 3 micrograms/day. Once the dose is stabilised, calcium levels may be measured every 2-4 weeks.

Indices of response, in addition to plasma calcium, may include alkaline phosphatase, parathyroid hormone levels, bone radiography and histological investigations. When there is biochemical or radiographic evidence of bone healing (or in hypoparathyroidism when calcium levels have normalised) the dose required for maintenance generally decreases to around 0.25 to 1 microgram/day. Should hypercalcaemia occur, Alfacalcidol should be stopped until plasma calcium returns to normal (usually about a week), and then restarted at one half of the previous dose.

Renal Osteodystrophy - Patients with already high plasma calcium levels may have autonomous hyperparathyroidism. In this situation they may not respond to alfacalcidol and other therapeutic measures may be indicated.

In patients with chronic renal disease it is particularly important to check the plasma calcium frequently because prolonged hypercalcaemia may further impair renal function.

Before and during Alfacalcidol treatment, the use of phosphate binding agents to prevent hyperphosphataemia may also be considered.

Hypoparathyroidism - Low plasma calcium levels may be restored to normal more quickly with Alfacalcidol than with parent Vitamin D. Severe hypocalcaemia is corrected more rapidly with higher doses of Alfacalcidol (e.g. 3-5 micrograms) together with calcium supplements.

Hyperparathyroidism - In patients needing surgery for primary or tertiary hyperparathyroidism, pre-operative treatment with Alfacalcidol for 2-3 weeks can reduce bone pain and myopathy without aggravating hypercalcaemia. To decrease the risk of post-operative hypocalcaemia, Alfacalcidol should be continued until the plasma alkaline phosphatase falls to normal or hypercalcaemia occurs.

Nutritional and Malabsorptive Rickets and Osteomalacia - Malabsorptive osteomalacia, which responds to large doses of intramuscular or intravenous parent Vitamin D, will respond to small oral doses of AlfaD. Nutritional rickets and osteomalacia can also be rapidly corrected with AlfaD.

Hypophosphataemic Vitamin D-Resistant Rickets and Osteomalacia - Normal doses of Alfacalcidol rapidly relieve myopathy when present, and increase calcium and phosphate retention. Phosphate supplements may also be required in some patients. Neither large doses of parent Vitamin D nor phosphate supplements are entirely satisfactory in these conditions.

Pseudo-Deficiency (D-Dependent Type1) Rickets and Osteomalacia - As with the nutritional conditions, similar oral doses of Alfacalcidol are effective in circumstances which would require high doses of parent Vitamin D.

Use in Children

Alfacalcidol Soft Gelatin Capsules are not indicated in children under 20 kg as the dosage cannot be titrated adequately.

Use in Elderly

Initiation of therapy requires a lower dose in elderly patients. The clinical manifestations of hypo- or hypercalcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

4.3 CONTRAINDICATIONS

Alfacalcidol should not be used by patients with evidence of Vitamin D toxicity or known hypersensitivity to the effects of Vitamin D or any of its analogues. Alfacalcidol Capsules contain arachis oil (peanut oil) and should not be used by patients with peanut allergy.

As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid Alfacalcidol Capsules.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Alfacalcidol increases the internal absorption of calcium and phosphate, serum levels of which should be monitored, particularly in patients with renal failure.

If hypercalcaemia or hypercalciuria occur this can be corrected rapidly by stopping treatment with Alfacalcidol and any calcium supplements until plasma calcium levels return to normal, usually in about a week. Alfacalcidol may then be restarted at half the last dose used.

Response to alfacalcidol may be impaired if the diet is markedly deficient in calcium.

Healing of bone lesions often indicates a decreased requirement for Alfacalcidol in which case appropriate dose adjustments should be made (see Posology and Method of Administration).

Alfacalcidol Capsules contain small amounts of ethanol (alcohol), approximately 1mg per capsule.

The capsule shell contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol may cause gastro-intestinal disturbance.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Hypercalcaemia in patients taking digitalis preparations may precipitate cardiac arrhythmias. Patients taking digitalis concurrently with alfacalcidol must therefore be closely monitored. Patients on barbiturates or other anticonvulsants may require an increased dose of Alfacalcidol to produce the desired effect.

Absorption of alfacalcidol may be impaired by concurrent use of mineral oil (prolonged use), colestyramine, colestipol, sucralfate or large amounts of aluminium-based antacids.

Caution should be exercised in the use of magnesium-based antacids or laxatives for patients taking alfacalcidol who are on chronic renal dialysis. Hypermagnesaemia may occur.

The risk of hypercalcaemia is increased in patients taking calcium-containing preparations or thiazide diuretics concurrently with alfacalcidol.

Alfacalcidol is a potent derivative of Vitamin D. Pharmacological doses of Vitamin D or its analogues should not be given during alfacalcidol treatment because of the possibility of additive effects and an increased risk of hypercalcaemia.

4.6 PREGNANCY AND LACTATION

There is insufficient evidence on which to assess the safety of alfacalcidol use during pregnancy, although it has been widely used for many years without apparent adverse effects. Animal studies have not revealed any hazard but as with all drugs, Alfacalcidol should only be used during pregnancy if treatment is essential and no better alternative is available.

Although not definitely established, it is likely that increased levels of 1,25-dihydroxyvitamin D₃ will be found in the breast milk of mothers treated with alfacalcidol. This might have an influence on calcium metabolism in a breast-fed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Adverse effects generally relate to abnormally elevated serum calcium levels leading to symptoms of anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised plasma and urine concentrations of calcium and phosphate. In the case of renal impairment, elevated serum phosphate levels may be induced by Alfacalcidol therapy. The dosage should be adjusted to the patient's requirements.

4.9 OVERDOSE

Excessive intake of vitamin D leads to the development of hypercalcaemia. Administration of Alfacalcidol should be stopped if hypercalcaemia occurs symptoms of which include anorexia, lassitude, nausea, vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised plasma and urine concentrations of calcium and phosphate. Severe hypercalcaemia may require treatment with general supportive measures, with intravenous fluids, with a loop diuretic or with corticosteroids.

In acute overdosage, early treatment with gastric lavage and/or the administration of mineral oil may reduce absorption and promote faecal elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: A11C C03 (Vitamin A and D, incl. combinations of the two, vitamin D and analogues).

When 1- α -hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D₃ production is reduced. Disorders in which this can occur include renal bone disease, hypoparathyroidism and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their correction but will respond to small doses of Alfacalcidol, which does not depend on the renal 1- α -hydroxylation process.

When using parent Vitamin D, the high dose and variable response time can lead to unpredictable hypercalcaemia which may take many weeks, sometimes months, to reverse. With Alfacalcidol, the more rapid onset of response allows better titration of dose and, if hypercalcaemia does occur, it can be reversed within days of stopping treatment.

5.2 PHARMACOKINETIC PROPERTIES

Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxy-vitamin D₃, the Vitamin D₃ metabolite which acts as a regulator of calcium and phosphate metabolism.

5.3 PRECLINICAL SAFETY DATA

There are no pre-clinical data of relevance to the prescriber, which are additional to that provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Capsule Contents

Citric Acid, Anhydrous (E330)

Propyl Gallate (E310)

α-Tocopherol (E307)

Ethanol, Anhydrous

Arachis Oil (peanut oil)

Soft Gelatin Capsule Shell

Gelatin

Glycerol

Sorbitol

Titanium dioxide (E171)

Red iron oxide (E172)

Printing Ink

Shellac

Black iron oxide

Propylene glycol

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

Cold form aluminium-aluminium blister strips each with 10 capsules, in packs of 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tenlec Pharma Ltd.

Hailsham,

East Sussex BN27 1PQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 19053/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2009

10 DATE OF REVISION OF THE TEXT

28/10/2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 1 Microgram Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains 1 microgram of alfacalcidol.

Each soft gelatin capsule also contains 98.8mg of Arachis oil (refined), 1.15mg ethanol and 4.53mg of sorbitol 70%.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Oval, opaque cream coloured, elastic soft gelatin capsule printed with "1.0" containing a clear, pale yellow, oily solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alfacalcidol is used for treating conditions in which calcium metabolism is disturbed due to impaired 1 α -hydroxylation and other disorders associated with Vitamin D resistance.

The main indications are:

- Renal osteodystrophy
- Hypoparathyroidism
- Hyperparathyroidism (with bone disease)
- Nutritional and malabsorptive rickets and osteomalacia
- Hypophosphataemic Vitamin-D resistant rickets and osteomalacia
- Pseudo-deficiency (D-dependent Type 1) rickets and osteomalacia

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

All indications -

Starting dose:

Children 20 kg and over:	1 microgram/day
Adults:	1 microgram/day
Elderly patients:	0.5 microgram/day

The dose should subsequently be adjusted according to the biochemical response to avoid hypercalcaemia. Plasma calcium levels (preferably corrected for protein binding) should initially be measured weekly. The dose of Alfacalcidol can be increased by increments of 0.25 to 0.5 micrograms/day. Most adults respond to doses of 1 to 3 micrograms/day. Once the dose is stabilised, calcium levels may be measured every 2-4 weeks. Indices of response, in addition to plasma calcium, may include alkaline phosphatase, parathyroid hormone levels, bone radiography and histological investigations. When there is biochemical or radiographic evidence of bone healing (or in hypoparathyroidism when calcium levels have normalised) the dose required for maintenance generally decreases to around 0.25 to 1 microgram/day. Should hypercalcaemia occur, Alfacalcidol should be stopped until plasma calcium returns to normal (usually about a week), and then restarted at one half of the previous dose.

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5 PHARMACOLOGICAL PROPERTIES

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ATC Code: A11C C03 (Vitamin A and D, incl. combinations of the two, vitamin D and analogues).

When 1- α -hydroxylation by the kidneys is impaired, endogenous 1,25-di-hydroxyvitamin D₃ production is reduced. Disorders in which this can occur include renal bone disease, hypoparathyroidism and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their correction but will respond to small doses of Alfacalcidol, which does not depend on the renal 1- α -hydroxylation process.

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Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxy-vitamin D₃, the Vitamin D₃ metabolite which acts as a regulator of calcium and phosphate metabolism.

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There are no pre-clinical data of relevance to the prescriber, which are additional to that provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Capsule Contents

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Propyl Gallate (E310)

α-Tocopherol (E307)

Ethanol, Anhydrous

Arachis Oil (peanut oil)

Soft Gelatin Capsule Shell

Gelatin

Glycerol

Sorbitol

Titanium dioxide (E171)

Yellow iron oxide (E172)

Printing Ink

Shellac

Black iron oxide

Propylene glycol

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

Cold form aluminium-aluminium blister strips each with 10 capsules, in packs of 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tenlec Pharma Ltd.

Hailsham,

East Sussex BN27 1PQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 19053/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2009

10 DATE OF REVISION OF THE TEXT

28/10/2009

ALFACALCIDOL 0.25 MICROGRAMS CAPSULES PL 19053/0010

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alfacalcidol 0.25, 0.5 and 1 microgram Capsules (Referred to as Alfacalcidol Capsules in the leaflet)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Alfacalcidol Capsules are and what they are used for
2. Before you take Alfacalcidol Capsules
3. How Alfacalcidol Capsules are taken
4. Possible side effects
5. Storing Alfacalcidol Capsules
6. Further information

1. WHAT ALFACALCIDOL CAPSULES ARE AND WHAT THEY ARE USED FOR

Each capsule contains 0.25, 0.5 or 1 microgram of alfacalcidol. Alfacalcidol is a vitamin D product that helps the body to use calcium and phosphate for healthy bones. Your medicine is used to treat renal (kidney) bone diseases as well as rickets, osteomalacia (which is a disease causing the bones to soften and weaken) and patients with high or low activity of the parathyroid gland. It is used to maintain normal calcium levels within the body.

2. BEFORE YOU TAKE ALFACALCIDOL CAPSULES

Do **not** take Alfacalcidol Capsules if:

- You are sensitive to any of the ingredients in the medicine (listed in section 6). These capsules contain small amounts of peanut oil (arachis oil), which may cause a severe allergic reaction in sensitive people.

Before taking Alfacalcidol Capsules, tell your doctor if:

- You have kidney problems

Taking Alfacalcidol Capsules with other medicines

Tell your doctor if you are taking or have recently taken any other medicines, including those obtained without a prescription. Such medicines include:

- Digoxin
- Barbiturates e.g. phenobarbital, or anticonvulsants (anti-epileptic medication) e.g. phenytoin
- Mineral oil, colestyramine, colestipol or sucralfate
- Large amounts of aluminium-containing antacids e.g. aluminium hydroxide
- Magnesium-containing antacids or laxatives e.g. magnesium hydroxide
- Preparations containing calcium e.g. calcium gluconate
- Diuretics ("water tablets") e.g. bendroflumethiazide

- Any other preparations containing vitamin D, e.g. ergocalciferol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Alfacalcidol Capsules are unlikely to affect your ability to drive or operate machinery

Important information about some of the ingredients of Alfacalcidol Capsules

The capsule contains small amounts of sorbitol, which should be avoided if you have an intolerance to fructose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. Sorbitol may cause stomach upset and diarrhoea.

These capsules contain arachis oil (peanut oil). If you are allergic to peanut or soya, do not use Alfacalcidol Capsules

Alfacalcidol Capsules contain small amounts of ethanol (alcohol), approximately 1mg per capsule.

3. HOW ALFACALCIDOL CAPSULES SHOULD BE TAKEN

Always take Alfacalcidol Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The capsules should be swallowed whole with a drink of water.

The usual starting dose is:

<u>Starting dose:</u>	<u>Alfacalcidol per day</u>
Adults	1.0 microgram
Children 20 kg and over	1.0 microgram
Children under 20 kg	Not recommended
The Elderly	0.5 microgram

At the beginning of your treatment calcium levels in your blood should be measured weekly.

The dosage can then be adjusted to achieve the correct response. Doses may be increased by 0.25 – 0.5 microgram per day. When the correct dosage has been found your calcium levels may be measured every 2 – 4 weeks.

If your diet is deficient in calcium, Alfacalcidol may not work as well.

Levels of phosphate in your blood may also be measured regularly, especially if you suffer from kidney problems.

If you take more Alfacalcidol Capsules than you should

If you (or someone else) swallow a lot of the capsules all together, or if you think a child has accidentally swallowed any of the capsules, contact your nearest hospital casualty department or your doctor immediately. If you or anyone else has taken too many capsules, there may be signs of nausea, vomiting, weakness, sweating, diarrhoea, headache, vertigo, thirst and excessive urination.

If you forget to take Alfacalcidol Capsules

If you forget to take a capsule, take one as soon as you remember, unless it is nearly time to take the next one. Do not take a double dose to make up for missed doses. Take the remaining doses at the correct time.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alfacalcidol can cause side effects, although not everyone gets these. Side effects are generally caused by having too much calcium in the blood.

- Feeling sick, stomach pains or diarrhoea
- General weakness, anorexia, thirst, weight loss
- Sweating, vertigo, dizziness, headache,
- Excessive urination

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING ALFACALCIDOL CAPSULES

Store in the original package and keep blisters in the outer carton. Keep them out of the reach and sight of children. Do not store above 25°C. Do not use after the expiry date shown on the outer packaging.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Alfacalcidol Capsules contain

The active ingredient is alfacalcidol. Each capsule contains 0.25, 0.5 or 1 microgram of alfacalcidol.

Other ingredients are citric acid, propyl gallate, α -tocopherol (vitamin E), ethanol and arachis oil (peanut oil). The capsule shell contains gelatin, glycerol and sorbitol, with shellac, black iron oxide (E172) and propylene glycol in the printing ink.

The Capsules also contain the following colours:

0.25 microgram - red iron oxide (E172).

0.5 microgram - titanium dioxide (E171) and red iron oxide (E172).

1 microgram - titanium dioxide (E171) and yellow iron oxide (E172).

What Alfacalcidol Capsules look like and contents of the pack

Alfacalcidol Capsules are soft gelatin capsules coloured reddish brown printed with "0.25" (0.25 microgram), pale pink printed with "0.5" (0.5 microgram) or cream printed with "1.0" (1 microgram). The product is available in blister packs. The pack size is 30 capsules.

Marketing Authorisation Holder

Tenlec Pharma Ltd.

Hailsham, East Sussex BN27 1PQ

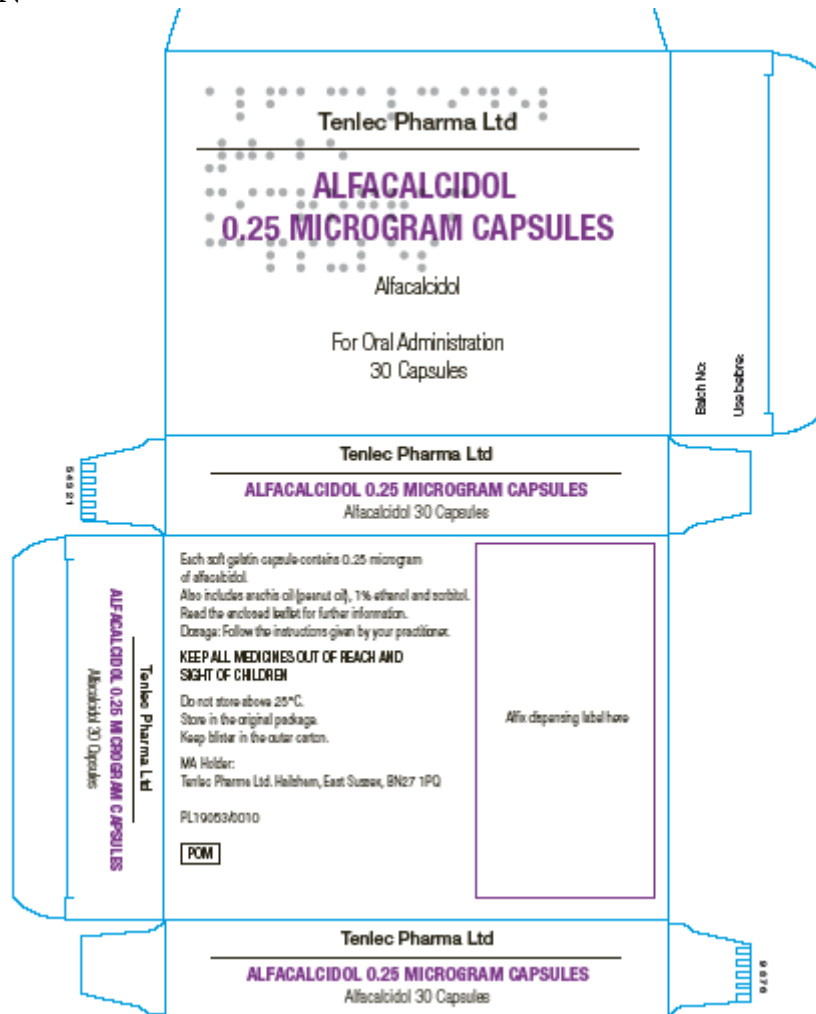
Manufacturer

TEVA Pharmaceutical Works plc, Debrecen, H-4042, Hungary.

This leaflet was last approved in

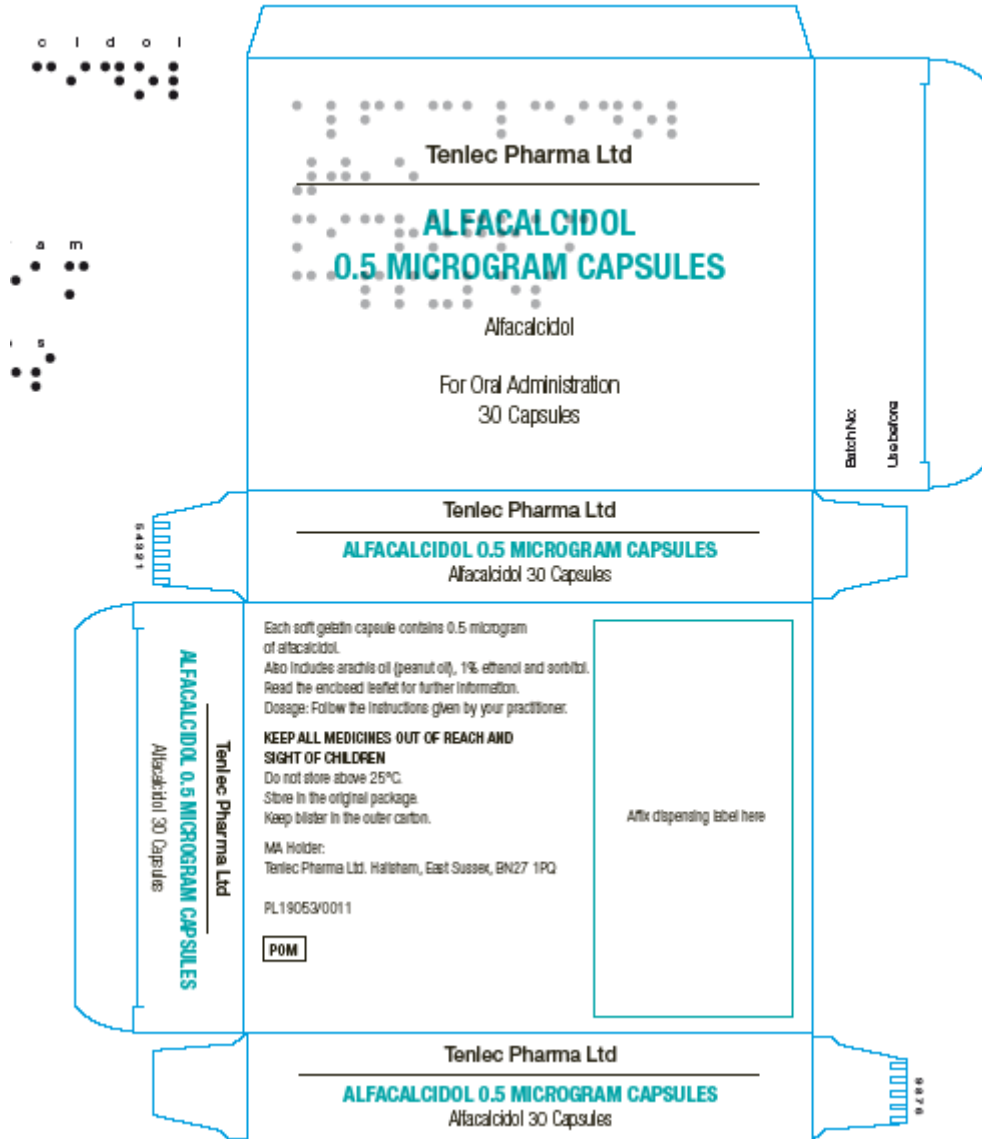
LABELLING

CARTON



BLISTER

Alfacalcidol 0.25 microgram Capsules MA Holder: Tenlec Pharma Ltd PL 19053/0010	Alfacalcidol 0.25 microgram Capsules MA Holder: Tenlec Pharma Ltd PL 19053/0010
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