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Public Assessment Report

Scientific discussion

Alfacalcidol Medreg 0,5 µg
Alfacalcidol Medreg 1 µg

SK/H/0305/001-002/DC

Date: 14.02.2025

This module reflects the scientific discussion for the approval of Alfacalcidol Medreg. The procedure was finalised at 09.10.2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alfacalcidol Medreg 0.5 µg and Alfacalcidol Medreg 1 µg, soft capsules from Medreg s.r.o.. for treatment of:

- renal osteodystrophy
- hyperparathyroidism (with bone disease)
- hypoparathyroidism
- pseudo-deficiency (D-dependent) rickets and osteomalacia
- hypophosphataemic vitamin D resistant rickets and osteomalacia

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The pharmaceutical form of Alfacalcidol Medreg is a soft capsule containing alfacalcidol as active substance, which belongs to vitamins.

0.5 µg
Description: Pink Opaque color oval shape soft gelatin capsule containing clear colorless liquid, (9.5 ± 1 mm long x 5.5 ± 1 mm width).

1.0 µg
Description: Brown Opaque color oval shape soft gelatin capsule containing clear colorless liquid, (9.5 ± 1 mm long x 5.5 ± 1 mm width).

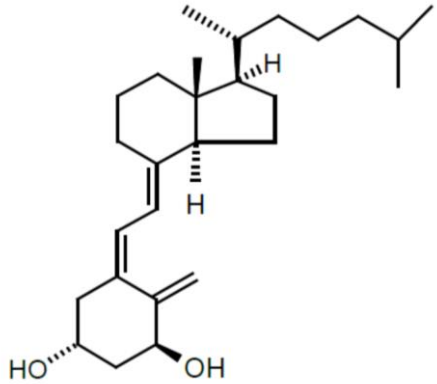
The excipients used in alfacalcidol capsules were selected based on the excipients used in the literature and drug-excipients compatibility study. Excipients (medium chain triglycerides, butylhydroxyanisole (E320), butylhydroxytoluene (E321), gelatin, glycerol, titanium dioxide, purified water) used in the formulation comply with the European Pharmacopoeia. Iron oxide black (E172) and iron oxide red (E172) comply with commission regulation EU 231/2012.
Container closure system for drug product is white, opaque PVC/PVDC/AL blister, packed in carton box.
Pack size: 28, 30, 56, 60, 90, 98 or 100 capsules.

II.2 Drug Substance

Alfacalcidol is described in the European Pharmacopeia monograph No. 1286. The drug substance alfacalcidol is manufactured by Carbogen Amcis B.V., The Netherlands. Quality of the drug substance is covered by CEP (R1-CEP 1998-097-Rev 09). Drug substance specification is in compliance with the current Ph. Eur. monograph 04/2022:1286 for alfacalcidol supplemented by GC test for residual solvents and by test for microbiological purity in compliance with Ph. Eur. 2.6.12 and 2.6.13. Microbiological tests are performed on one batch per year by drug substance manufacturer.

Non-Proprietary Name (INN)	Alfacalcidol
Compendial Names	European Pharmacopoeia Name

Chemical Names	(5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β-diol (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3-diol 1α-Hydroxycholecalciferol



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

Relative Molecular Mass: 400.6 g/mol

Appearance	White to almost white crystals
Solubility (at 20°C)	Alfacalcidol is practically insoluble in water; freely soluble in ethanol (96 per cent); soluble in fatty oils.

The drug substance is packed under nitrogen in a glass vial closed by a rubber stopper and an aluminium cap, in a seal bag, placed in a cardboard box; container closure system is declared in CEP certificate. Certificate declares that during manufacture of drug substance sheep wool is used and that alfacalcidol meets the criteria described in the current version of the monograph *Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483* of the European Pharmacopeia. Ph. Eur. analytical methods and methods included in CEP certificate are used for drug substance control.

Re-test period is not included in the CEP certificate. Stability studies in glass vials were conducted on three drug substance batches. Re-test period in glass vials is 36 months at 2-8°C.

II.3 Medicinal Product

Drug product is soft capsule of 0.5 µg and 1.0 µg strength manufactured by Olive Healthcare, India. For both strengths capsule size is the same, they are distinguished by colour; 0.5 µg soft capsule is pink colour, and 1.0 µg soft capsule is brown. Total weight of medicament and assay of antioxidants (butylhydroxyanisole, butylhydroxytoluene) are identical for both strengths, content of triglycerides, medium chain varies. Composition of capsule shells differs in colorant and slightly in water quantity.

The aim of formulation development was to manufacture a generic version of One Alpha of Leo Pharma B.V. The development of the product has been described, the choice of excipients is justified, and their functions explained. Gelatin mass, encapsulation process, drying process and capsule polishing were considered during manufacturing process optimization.

Manufacturing process of soft capsules was described in detail and consists of following steps: gelatin mass manufacturing, medicament manufacturing, encapsulation, drying, polishing/wiping and packaging. Holding time study was conducted on gelatin mass, medicament, and bulk capsules. The shelf life of the drug product is set in accordance with the criteria of the EMA NfG on start of shelf-life of the finished dosage form.

Specification for drug product (release and shelf-life) contains relevant specification parameters for the proposed dosage form – soft capsules and limits are in line with ICH Q6A guideline.

The bulk capsules are packed into clear LDPE bag, placed in black LDPE bag and closed. Container closure system for drug product i.e opaque PVC/PVDC –AL blister is well justified.

Based on stability results from long-term stability covering 48 months and accelerated studies covering 6 months, the approved shelf-life of the drug products is 48 months and they are to be stored in the original package in order to protect from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Alfacalcidol Medreg 0.5 µg and 1.0 µg are of sufficient quality in view of the present European regulatory requirements.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of alfacalcidol are well known. As alfacalcidol is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Alfacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin D. This is an active 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. Thus, the main mechanism of action is based on increasing the levels of circulating 1,25-dihydroxyvitamin D, thereby increasing the absorption of calcium and phosphates from the intestine. Bone mineralization is supported, circulating parathyroid hormone levels are reduced and bone resoption is inhibited.

III.2 Pharmacology

The applicant has provided a detailed summary of the nonclinical primary pharmacology for the active substance of Alfacalcidol Medreg 0,5 µg; Alfacalcidol Medreg 1 µg. In addition, sections on secondary pharmacology, safety pharmacology, and pharmacodynamics drug interactions have also provided sufficient data.

The respiratory, CNS, CVS, and renal effects were presented in the safety pharmacology section. All the presented findings are already well-documented and characterized since the active substance is a widely studied compound with known pharmacological effects on the vital organ systems (CNS, CVS, RESP) and supplemental systems (gastrointestinal, renal). The adverse effects observed on the safety pharmacology battery of screened organ systems are mostly signs of hypervitaminosis D, hypercalcaemia and further calcification of the soft tissues, and hypercalciuria.

The safety concerns arising from the occurrence of hypervitaminosis D and hypercalcaemia are adequately reflected in the treatment management stated in the SmPC (dose adjustment according to biochemical response, monitoring of serum calcium, cessation of treatment in cases of hypercalcaemia, frequent plasma calcium measurements in patients with chronic renal failure). This drug product is also contraindicated in cases of hypercalcaemia and metastatic calcification.

III.3 Pharmacokinetics

Numerous in vitro and in vivo studies have carried out extensive evaluations of the PKs of alfacalcidol and its active metabolite, calcitriol. The applicant has provided an overview of the nonclinical pharmacokinetics of alfacalcidol based on published literature.

The applicant provided adequate pharmacokinetic data dedicated to the absorption, distribution, metabolism and excretion of active substance as in relevant animal species.

III.4 Toxicology

Single dose toxicity data being considered, alfacalcidol showed a very low toxicity potential in acute toxicity studies when comparing the toxic doses of the drug given to dogs and rodents (which are equivalent to hundreds or thousands of times the human daily dose) with the recommended posology used in clinical settings.

The genotoxicity tests results, along with alfacalcidol's well-established safety profile and clinical record, exclude a risk of genotoxicity or mutagenicity. Reproductive and developmental toxicity studies have not revealed any safety concerns. The local tolerance studies provided have not revealed any issues to be further discussed. The excipients qualitative and quantitative safety profiles have been adequately and extensively discussed. No safety concerns related to the excipients´ safety when used in the recommended dosing regimen are raised. Similarly, impurities identified in both the drug's drug substance and its final drug product pose no safety risk.

Overall, the product does not present any toxicological concerns.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Based on the applicant´s characterization of the nature of compound, the further ERA and PBT assessments are not required.

III.6 Discussion on the non-clinical aspects

Submitted non-clinical data are adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the clinical pharmacology, efficacy and safety was adequate.

The pharmacological properties as well as safety and efficacy information were documented and the facts were supported by appropriate literature references

IV.2 Pharmacokinetics

Due to the unavailability of many full texts and the type of the application where the applicant does not have access to the full documentation, information on analytical methods and pharmacokinetic data analysis is very scarce. Considering the WEU character of this application, this limitation of literature is acceptable.

The Applicant provided an extensive discussion of bridging to already authorised products. The bridging approach is supported.

The Applicant provided disintegration studies over pH 1.2 to 6.8 with the product Etalpha (Leo Pharma B.V., Amsterdam), that showed similar disintegration times. This indicates a comparable and rapid disintegration.

The Applicant summarised composition of over 10 different products authorised in the EU containing alfacalcidol. This summary shows that products may differ in type of oil/s chosen for dissolution of

alfacalcidol and excipients in gelatine capsule shell. The Applicant provided a thorough discussion also with PK studies that type of oil used for dissolution of alfacalcidol does not impact bioequivalence of soft shell capsules containing alfacalcidol.

IV.3 Pharmacodynamics

The applicant has submitted a review of literature in order to demonstrate PD properties. Alfacalcidol is converted to calcitriol in the liver or bone to exert its pharmacological actions. The first step involved in the activation of vitamin D3 is a 25-hydroxylation which is catalysed by the 25-hydroxylase and then by other enzymes. Alfacalcidol has been shown to induce active absorption of Ca and phosphate, improve mineralisation of the skeleton.

The potential PD interactions between alfacalcidol and other drugs have been investigated and presented in the PI texts of other approved alfacalcidol-containing oral preparations.

IV.4 Clinical efficacy

The applicant has submitted a review of literature to demonstrate efficacy in given indications.

IV.5 Clinical safety

The applicant has submitted a review of literature in order to demonstrate safety of alfacalcidol. In general, oral alfacalcidol has been well-tolerated in controlled clinical trials, across the range of therapeutic dosages and has shown a favourable safety profile over long-term treatment periods. The proposed safety information in the product information is appropriate.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to alfacalcidol.

IV.7 Discussion on the clinical aspects

Submitted clinical data are adequate to support the indications.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk assessment is considered positive.
The dossier is generally well presented, and the process appears to be well controlled. The application is acceptable from the quality perspective.
There are no objections to the dossier of Alfacalcidol Medreg from a non-clinical point of view. From the clinical perspective, submitted clinical data are adequate to support the indication.
SmPC, PIL and labelling are satisfactory.