COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hidroferol 0.266 mg soft capsules (calcifediol)

NL/H/5606/001/DC

Date: 22 June 2022

This module reflects the scientific discussion for the approval of Hidroferol 0.266 mg soft capsules. The procedure was finalised on February 2017 with Spain as RMS (ES/H/0412/001/DC). The current RMS is the Netherlands (NL/H/5606/001/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Hidroferol 0.266 mg soft capsules, from Faes Farma, S.A.

The product is indicated in adults for:
Treatment of vitamin D deficiency, in those cases where the initial administration of high doses is required or administration spaced in time is preferred, as in the following situations:

- As adjuvant for the treatment of osteoporosis
- In patients with malabsorption syndrome
- Renal osteodystrophy
- Bone diseases induced by treatment with corticosteroid drugs.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Hidroferol 0.266 mg oral solution, which has been registered in Spain by Faes Farma, S.A. since 1977. In the Netherlands, Hidroferol 0.266 mg oral solution has been registered since 17 November 2020 by the mutual recognition procedure NL/H/5606/001.

The reference member state (RMS) of the initial procedure was Spain and the concerned member states (CMS) involved in this procedure were Belgium, France, Germany, Italy, Poland and Portugal. The role of RMS was transferred to the Netherlands on 16 June 2022.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Hidroferol is an orange, oval soft gelatine capsule containing a clear, low viscous and free from particles liquid. Each capsule contains as active substance 0.266 mg of calcifediol, equivalent to 15.960 international units of vitamin D.

The soft capsules are packed in either PVC-PCDC/Al or Al/Al blisters.

The excipients are:
Capsule content – calcifediol, anhydrous ethanol and medium-chain triglycerides.

Capsule shell – gelatine, glycerol, sorbitol, titanium dioxide (E-171) and sunset yellow S (E-110).

II.2 Drug Substance

Calcifediol is a known active substance described in Ph.Eur. A Ph.Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient.
The CEP does not include re-test period but stability data have been included in the dossier to support the proposed the re-test period.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development has been adequately described.
The proportion of each solvent in cosolvent mixture has been discussed. The composition of capsule shell has been justified.
Test for disintegration and dissolution of soft capsules has been performed.
The photostability of calcifediol concern has been discussed along the production process.

Manufacturing process
The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Control of excipients
The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient). All the gelatin sources used for capsules have CEP on TSE risk evaluation.

Quality control of drug product
The specifications proposed for the soft capsule is adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.
The components of the container closure system comply with the specifications established in the applicable Ph. Eur. Monographs and/or EU directives on foodstuff contact.

Stability of drug product
The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Due to the origin and type of tissues of raw material and the manufacturing process applied, the CEP indicates than the active substance 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 Pharmacopoeia, current edition including supplements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Hidroferol has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Hidroferol is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Hidroferol oral solution which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcifediol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Since the dossier is identical to the dossier approved for the reference product Hidroferol 0.266 mg oral solution and have an identical Module 3, the active pharmaceutical ingredient used, the manufacturing process and manufacturing site for the finished dosage form being the same. A bioavailability study is therefore not required to demonstrate bioequivalence, and none is provided in this application.

IV.3 Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.
No additional risk minimization activities were required beyond those included in the product information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Hidroferol 0.266 mg oral solution. No new clinical studies and no bioequivalence study were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Hidroferol 0.266 mg soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Hidroferol 0.266 mg oral solution. Hidroferol oral solution is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hidroferol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on February 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
ES/H/0412/001/IB/001	Change in the (invented) name of the medicinal product in Portugal	Y	20-9-2017	Approved	
ES/H/0412/001/IA/002	Replacement or addition of a secondary packaging site	-	20-9-2017	Approved	
ES/H/0412/001/IB/003	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product; other variation	-	20-11-2017	Approved	
ES/H/0412/001/IB/004	Implementation of change(s) for which no new additional data is required to be submitted by the MAH	-	8-6-2018	Approved	
ES/H/0412/001/IA/005	Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	-	6-7-2018	Approved	
ES/H/0412/IB/006/G	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	11-10-2018	Approved	
ES/H/0412/001/IA/007	Minor changes to an approved test procedure	-	22-8-2019	Approved	
ES/H/0412/001/IB/008	Change of the (invented) name of the medicinal product in Belgium	Y	17-9-2019	Approved	
ES/H/0412/001/IA/009	Updated certificate from an already approved manufacturer	-	5-11-2019	Approved	
ES/H/0412/IB/010/G	- Addition of a new specification parameter to the specification with its corresponding test method - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	-	23-4-2020	Approved	

	- Minor changes to an approved test procedure				
ES/H/0412/001/E/001	Adding of new CMS Belgium, Bulgaria, Estonia, Latvia, Lithuania, Luxembourg, the Netherlands and Romania	Y	22-8-2020	Approved	
ES/H/0412/001/WS/011	Other variation Type II C.I.z	-	30-8-2021	Approved	
ES/H/0412/001/IB/012	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product; other variation	-	5-2-2021	Approved	
ES/H/0412/001/R/001	Renewal	Y	24-6-21	Approved	-
ES/H/0412/IB/013/G	- Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location - Introduction of new summary Pharmacovigilance System Master File (sPSMF) from the new Marketing Authorisation Holder in CMS.		22-10-2021	Partially approved	The change of the invented name has been refused. The MAH requested the same name for CMS Lithuania, Latvia, and Estonia.
ES/H/0412/IB/014/G	Change of (invented) name in CMS Lithuania, Latvia, and Estonia	Y	11-3-2022	Approved	