IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Colecalciferol Aristo 20,000 IU soft capsules
Colecalciferol
PA1983/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Colecalciferol Aristo 20,000 IU Soft Capsules, from Aristo Pharma GmbH on 23rd February 2018 for: Initial treatment of symptomatic vitamin D deficiency in adults.

This application for a marketing authorisation was submitted as a decentralised procedure application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application. The RMS is IE, with the DE as sole CMS.

This is a prescription-only medicinal product.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	**Colecalciferol Aristo 20,000 IU Soft Capsules**
Name(s) of the active substance(s) (INN)	Colecalciferol
Pharmacotherapeutic classification (ATC code)	A11CC05
Pharmaceutical form and strength(s)	Soft Capsules, 20,000 IU
Marketing Authorisation Number(s) in Ireland (PA)	PA1983/002/001
Marketing Authorisation Holder	Aristo Pharma GmbH Wallenroder Straße 8-10 13435 Berlin, Germany
MRP/DCP No.	IE/H/476/001/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Colecalciferol Aristo 20,000 IU Soft Capsules.

II.2 Drug substance

The active substance is cholecalciferol, an active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The capsules contain 20,000 IU of colecalciferol (equivalent to 500 micrograms Vitamin D3).
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)
All ingredients comply with the Ph. Eur.

P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Colecalciferol Aristo 20,000 IU Soft Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as amended, a well-established use application. Vitamin D3 has been in well-established use within the European Union for more than ten years, demonstrating a recognised efficacy and safety profile. A non-clinical overview has been provided, it is based on relevant published literature and written by an appropriately qualified person.

III.2 Pharmacology
Vitamin D3 (Colecalciferol) plays an important role in bone metabolism and in maintaining levels of calcium and phosphorous. It is biologically inactive and requires metabolism, mainly within in the liver and kidney, to be converted to the hormonal form 1,25 dihydroxycolecalciferol (1,25(OH)2D). Activation of the vitamin D receptor (VDR) by 1,25 (OH)2D within cells of the intestine, bone, kidney and parathyroid gland has an effect on the homeostasis of serum calcium and phosphorous levels, and as such on bone mineralization and remodelling.

III.3 Pharmacokinetics
No new non-clinical pharmacokinetics studies have been submitted. The profile of Vitamin D3 is well characterised in the published literature and an adequate overview has been submitted.

III.4 Toxicology
No new non-clinical toxicity studies have been submitted. The toxicity profile of Vitamin D3 is well characterised in the published literature. Teratogenicity has been observed in animal studies, but only at doses far higher than the human therapeutic dose.
There is no risk indicated with respect to general toxicity, genotoxicity, carcinogenicity or reproductive and developmental toxicity.

III.5 Ecotoxicity/environmental risk assessment
An Environmental Risk Assessment (ERA) was submitted by the applicant. The ERA indicates a logKow of 7.29 for colecalciferol, which matches the literature value of 7.5 within ± 0.3. Both the measured and literature value logKow are above the threshold value of 4.5 to trigger a step-wise screening for persistence of bioacculation and toxicity. However, the PECsurfacewater is 0.00125µg/L, which is below the trigger value of 0.01µg/L indicating that no other environmental concerns are apparent.

According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00) vitamins due to their nature are unlikely to result in a significant risk to the environment. Also, it is expected that the product will substitute parts of the existing use and prescriptions of the currently marketed vitamin D products. No changes in a potential environmental risk that are not already known for vitamin D are to be anticipated.

III.6 Discussion on the non-clinical aspects

Vitamin D3 has been in well-established use within the European Union for more than 10 years, demonstrating a recognised efficacy and safety profile. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. No new nonclinical studies were submitted. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate. An environmental risk assessment for Vitamin D3 was submitted and no environmental concerns are apparent.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is based on well-established use and therefore the clinical dossier is based upon published literature. Colecalciferol (cholecalciferol) is a well-known active substance with established efficacy and tolerability.

IV.2 Pharmacokinetics

The applicant provided an adequate overview of the pharmacokinetics of various oral formulations of colecalciferol where it is ascertained that fat-soluble vitamin D3 is absorbed through the small intestine in the presence of bile acids with the help of micellum and enters into the blood through lymphatic circulation. The administration with the major meal of the day might therefore facilitate the absorption of vitamin D3 as is recommended in the product information.

The proposed formulation has similar excipients to other approved colecalciferol formulations and are therefore not expected to affect bioavailability.

Vitamin D and its metabolites are excreted mainly in the bile and faeces.

IV.3 Pharmacodynamics

The pharmacodynamics of colecalciferol has been adequately discussed by the applicant and has been based on published literature. Section 4.5 of the SmPC reflects the known interactions of vitamin D with other medicinal products.

IV.4 Clinical Efficacy

Initial treatment of symptomatic vitamin D deficiency in adults:

The applicant has supplied summaries of numerous studies with vitamin D supplementation for the treatment of vitamin D deficiency in adults. Furthermore, there are numerous high-dose formulations already licensed in the community for the treatment of vitamin D deficiency. There are many different clinical guidelines for Vitamin D use by member states and the agreed SmPC caters for this.

IV.5 Clinical Safety

Based on the clinical studies provided by the applicant, the safety of the capsules containing 20000IU of colecalciferol is considered well-established. The applicant has given an adequate overview of the safety of colecalciferol. The SmPC and PL contain the relevant safety warnings and are generally in line with other licensed colecalciferol products.

Pharmacovigilance System

The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

· PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

· For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
· For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

This application is based on well-established use and therefore the clinical dossier is based upon published literature.

Colecalciferol is a well-known active substance with established efficacy and tolerability.

V. OVERALL CONCLUSIONS

The applicant has adequately supported the proposed indications and posology in adult patients:

Initial treatment of symptomatic vitamin D deficiency in adults:
The applicant has supplied summaries of numerous studies with vitamin D supplementation for the treatment of vitamin D deficiency in adults. Furthermore, there are numerous high-dose formulations already licensed in the community for the treatment of vitamin D deficiency. There are many different clinical guidelines for Vitamin D use by member states and the agreed SmPC caters for this.

Undesirable effects:
The following undesirable effects are mentioned in the proposed SmPC similar to other approved colecalciferol products: hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea, pruritus, rash and urticaria.

Acute or chronic overdose of vitamin D can cause hypercalcaemia. Symptoms of hypercalcemia are tiredness, headache, muscle and joint pain, muscle weakness, psychiatric symptoms (e.g., euphoria, dazedness, and disturbed consciousness), nausea, vomiting, lack of appetite, weight loss, thirst, polyuria, formation of renal calculi, nephrocalcinosis, extraosseous calcification and kidney failure, changes in ECG, arrhythmias, and pancreatitis.
In isolated cases their course has been described as fatal. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia.

Conclusion:
The overall assessment outcome of Colecalciferol Aristo 20,000 IU Soft Capsules, from Aristo Pharma GmbH, is positive.

The applicant has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Colecalciferol Aristo 20,000 IU Soft Capsules demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

18.10.2022