IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Colecalciferol 3000 IU/ml oral solution
Colecalciferol
PA22697/007/001

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

This product was initially authorised under procedure number UK/H/5521/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0778/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/007/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Colecalciferol Oral Solution (PL 39307/0020; UK/H/5521/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for treatment and prevention of vitamin D deficiency in adults, elderly and children over 12 years of age.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

In its biologically active form vitamin D_3 stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D_3. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D_3.

Bibliographic data on colecalciferol have been submitted to support this application. No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 30 December 2014. After a subsequent national phase, a licence was granted in the UK on 21 January 2015.

II. QUALITY ASPECTS

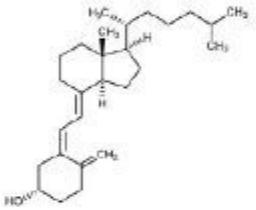
II QUALITY ASPECTS

II.1 Introduction

Each ml of solution contains 3000IU colecalciferol. Other ingredients consist of the following pharmaceutical excipients refined almond oil, refined sunflower oil and arachis oil (peanut oil). The finished product is packed into amber (Type III) glass bottles with high-density polyethylene (HDPE) expanded polyethylene (EPE) wadded, tamper evident, child-resistant screw on white plastic polypropylene caps. The bottle is packed into a cardboard box together with a dosing device which is a 1ml polypropylene oral syringe with 0.01 ml graduation mark and low-density polyethylene (LDPE) adaptor. The product is available in 100 ml size bottles. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN	Colecalciferol
Ph.Eur	Cholecalciferol concentrate (oily form)
Chemical name:	(5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3β-ol.
Structural formula:	



Molecular formula:	$C_{27}H_{44}O$
Molecular Mass:	384.7 g/mol.
Appearance:	Clear, yellow liquid.
Solubility:	Practically insoluble in water, slightly soluble in anhydrous ethanol, miscible with solvents of fats. Partial solidification may occur, depending on the temperature.

Cholecalciferol concentrate (oily form) is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, cholecalciferol concentrate (oily form), are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral solution containing 3000IU colecalciferol per ml of solution.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs
Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011).

A Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE) statement has been issued by the supplier to confirm that Vitamin D_3 is prepared synthetically in a process that includes wool grease (lanolin) from healthy live sheep from category A and B countries that does not present a risk of BSE/TSE contamination.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale batch size and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months for the unopened bottle and an in-use shelf life of 60 days once the bottle has been opened (discard contents 60 days after first opening) with the storage conditions 'Do not store above 25°C. Store in the original package. Keep the bottle in the original carton in order to protect from light.'

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of colecalciferol are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

An ERA is not required for this product as vitamins are exempt, in accordance with the Committee for Medicinal Products for Human Use (CHMP) "Guideline on the environmental risk assessment of medicinal products for human use."

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical pharmacology data, efficacy data or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of colecalciferol.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of colecalciferol is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical safety

No new safety data were submitted and none were required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profile of colecalciferol is well-known.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Colecalciferol Oral Solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns as approved in the RMP:

Summary of safety concerns	
Important identified risks	• Allergic reactions (Hypersensitivity) • Increased blood calcium levels (Hypercalcaemia) • Increased urine calcium levels (hypercalciuria) • Use in patients with kidney impairment [including kidney stones] (Use in patients with renal impairment [including nephrolithiasis and nephrocalcinosis]) • Use in patients with increased level of vitamin D (Hypervitaminosis D) • Use in patients with conditions that modify vitamin D breakdown including sarcoidosis (Use in patients with conditions that modify Vitamin D metabolism including sarcoidosis) • Interaction with thiazide diuretic (water pills) • Interaction with cardiac glycosides (heart failure medicine)
Important potential risks	• Use in pregnancy and lactation • Overdose
Important missing information	• None

Summary table of risk minimisation measures as approved in the RMP:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity	The risk of hypersensitivity associated with the use of the drug product is described in the SPC Section 4.3 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.	None
Hypercalcaemia	The risks of hypercalcaemia associated with the use of the drug product and risks associated with the use of the drug product in patients with diseases and/or conditions in which hypercalcaemia is present are described in the SPC Section 4.3, 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise these risks.	None
Hypercalciuria	The risks of hypercalciuria associated with the use of the drug product and risks associated with the use of the drug product in patients with diseases and/or conditions in which hypercalciuria is present are described in the SPC Section 4.3 and 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	
Use in patients with renal impairment (including nephrolithiasis and	The risks associated with the use of the drug product in patients with renal impairment	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
nephrocalcinosis)	(including nephrolithiasis and nephrocalcinosis) are described in the SPC Section 4.2, 4.3 and 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	
Use in patients with hypervitaminosis D	The risk associated with the use of the drug product in patients with hypervitaminosis D are described in the SPC Section 4.3, 4.9 and 5.3, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with conditions that modify vitamin D metabolism including sarcoidosis	The risks associated with the use of the drug product in patients with conditions that modify Vitamin D metabolism including sarcoidosis are described in the SPC Section 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise these risks.	None
Interaction with thiazide diuretic	The risks associated with interaction of the use of the drug product with thiazide diuretic are described in the SPC Section 4.5, and appropriate advice is provided to the prescriber to minimise these risks.	None
Interaction with cardiac glycosides	The risks associated with interaction of the use of the drug product with cardiac glycosides are described in the SPC Section 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risk		
Use in pregnancy and lactation	The risks associated with the use of the drug product during pregnancy and lactation are described in the SPC Section 4.6 and 5.3, and appropriate advice is provided to the prescriber to	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	minimise these risks.	
Overdose	The risks of overdose associated with the use of the drug product are described in the SPC Section 4.9 and 5.3, and appropriate advice is provided to the prescriber to minimise these risks.	None
Missing information		
• None		

IV.7 Discussion on the clinical aspects

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for this application does support the claim of well-established use for the sought indication of the treatment and prevention of vitamin D deficiency in adults, elderly and children over 12 years of age.

The grant of a marketing authorisation is recommended for this application.

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, as amended. The language used for the purpose of user testing the PIL was English.

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.*

V. OVERALL CONCLUSIONS

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with colecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

24/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5521/1/DC to IE/H/0778/1/DC			