IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Colecalciferol EQL Pharma 2000 IU tablet
Colecalciferol
PA22981/001/002

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 EQL Pharma 800 IU Tablet and Colecalciferol EQL Pharma 2000 IU Tablet, from EQL Pharma AB on 9th July 2021 for:

800 IU:

- Prevention of vitamin D deficiency in adults, elderly and adolescents with an identified risk.
- Treatment of vitamin D deficiency in adults, elderly and adolescents. Vitamin D deficiency is defined as serum levels of 25-hydroxycolecalciferol (25(OH)D) < 25 nmol/l.
- In addition to specific osteoporosis treatment of adult and elderly patients who are at risk of vitamin D deficiency, preferably in combination with calcium.

2000 IU:

- Treatment of vitamin D deficiency in adults, elderly and adolescents. Vitamin D deficiency is defined as serum levels of 25-hydroxycolecalciferol (25(OH)D) < 25 nmol/l.

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 CMS' NL, NO and SE.

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 EQL Pharma 800 IU Tablet Colecalciferol EQL Pharma 2000 IU Tablet
Name(s) of the active substance(s) (INN)	Colecalciferol
Pharmacotherapeutic classification (ATC code)	A11CC05
Pharmaceutical form and strength(s)	800 IU Tablet 2000 IU Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22981/001/001-002
Marketing Authorisation Holder	EQL Pharma AB
MRP/DCP No.	IE/H/1094/001-002/DC
Reference Member State	IE
Concerned Member State	NL NO SE

II. QUALITY ASPECTS

This application is for Colecalciferol EQL Pharma 800 IU Tablet and Colecalciferol EQL Pharma 2000 IU Tablet.

II.2 Drug substance

The active substance is Cholecalciferol, an established 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.

The chemical-pharmaceutical documentation in relation to the drug substance Cholecalciferol is of sufficient quality in view of the present European regulatory requirements

II.3 Medicinal product

P.1 Composition

Each tablet of Colecalciferol EQL Pharma 800 IU Tablets contains colecalciferol (vitamin D_3) 800 IU (equivalent to 20 microgram vitamin D_3)

Each tablet of Colecalciferol EQL Pharma 2000 IU Tablets contains colecalciferol (vitamin D_3) 2000 IU (equivalent to 50 microgram vitamin D_3).

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

A description and flow-chart of the manufacturing method has been provided and is satisfactory. In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications. Magnesium Stearate is from animal origin. None of the other excipients used in the manufacturing of colecalciferol tablets are from human or animal origin. The TSE-BSE Certificate for Magnesium Stearate is provided.

P.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the Ph. Eur. requirements for "Tablets" and the standard requirements associated with tablets for oral use. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory description and validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

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. and 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 demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in sections 6.3 and 6.4 of the Summary of Product Characteristics (SPC).

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 EQL Pharma 800 IU Tablet and Colecalciferol EQL Pharma 2000 IU Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This is an abridged application for marketing authorisation of Colecalciferol EQL Pharma in 800 IU and 2000 IU tablets through the decentralised procedure, in accordance with Article 10a of Directive 2001/83/EC as amended (well-established use). A nonclinical overview based on literature review was provided in support of this marketing authorisation application, which is acceptable. The GLP status of data from the published scientific literature cannot be verified.

III.2 Pharmacology

The pharmacology of colecalciferol is well known and well described in the literature. Given the extent of clinical use data available for this well-established use product, further non-clinical studies would not add value to the safety assessment for colecalciferol at this time.

Data from the published scientific literature describe endogenous Vitamin D3 production in the skin. Upon irradiation, 7-dehydrocholesterol produces pre-vitamin D3 which undergoes a temperature-sensitive rearrangement of three double bonds to form vitamin D3. Vitamin D can also be taken in the diet and the two hydroxylation processes required to activate exogenous cholecalciferol are described in the scientific literature. Cholecalciferol ingested via dietary intake or supplementation is hydroxylated in the liver and kidney, ultimately yielding 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), which is the biologically active form of vitamin D. Upon binding to vitamin D receptors, 1,25-dihydroxycholcalciferol promotes calcium and phosphate absorption from the small intestine, increases bone mineral density by suppressing bone resorption, and increases phosphate secretion in the renal tubule.

III.3 Pharmacokinetics

Colecalciferol is a widely used and well-known active substance. Given the extent of clinical use data available for this well-established use product, further non-clinical pharmacokinetic studies are not required.

Data from the scientific literature indicate Vitamin D3 absorption in vivo is mediated by passive diffusion.Data in rodents indicate vitaminD3 is taken up by the enterocytes by a non-saturable passive diffusion mechanism showing no evidence for carrier mediation. The rate of intestinal uptake is highest in the proximal and medial segments of the small bowel. Cholecalciferol is hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol). This compound undergoes further hydroxylation in the kidneys by the enzyme vitamin D1-hydroxylase to form the active metabolite 1,25- dihydroxycholecalciferol (calcitriol). Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status.

III.4 Toxicology

The non-clinical overview of the toxicology of colecalciferol has briefly addressed the repeat-dose toxicity, genotoxicity and reproductive and developmental toxicity of colecalciferol by reviewing the published literature on these topics. Cholecalciferol (vitamin D3)-related changes in a 26-week, repeated-dose oral toxicity study in rats consisted of nephrocalcinosis and pheochromocytomas in the adrenal medulla. These changes were observed at doses ≥ 5000 IU/kg/day. Genotoxicity data from the literature indicate that cholecalciferol is not genotoxic and the carcinogenic potential of cholecalciferol has not been studied in rodents. The overview of reproductive and developmental toxicity from the literature indicates teratogenicity in the offspring of pregnant rabbits administered large doses of vitamin D, with lesions anatomically similar to those of supravalvular aortic stenosis reported. Relevant findings regarding teratogenic effects associated with very high dose vitamin D have been included in section 4.6 and 5.3 of the SmPC, as they may be relevant for overdose situations.

III.5 Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, colecalciferol is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Colecalciferol is a widely used and well-known active substance and the pharmacodynamic, pharmacokinetic and toxicological properties of colecalciferol are well-known, therefore additional non-clinical safety studies have not been conducted and none are required. A nonclinical overview based on literature review was provided in support of this marketing authorisation application, which is acceptable.

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

There is no pharmacokinetic data specific for the currently applied product, which is acceptable. Due to the nature of the active substance, it is not considered necessary to compare the bioavailability of vitamin D from the new product with that from existing vitamin D containing products on the market. The product is intended to be a complement to dietary vitamin D3, which might be highly variable, and a potential minor difference in *in vivo* release properties from two different dosage forms would not be expected to lead to a different therapeutic profile. Moreover, as the absorption of vitamin D3 is controlled by a number of physiological processes and factors, the true absorption of this partly endogenous substance may be difficult to determine in a bioavailability study.

Absorption

Vitamin D is absorbed through the small intestine in association with lipids and with the aid of bile salts; it is then taken up in the lymph.

Distribution

Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol is converted in the liver by hydroxylation to 25-hydroxycolecalciferol. It is then further converted in the kidneys to 1,25- dihydroxycolecalciferol. 1,25-dihydroxycolecalciferol is the active metabolite responsible for increasing calcium absorption. Vitamin D, which is not metabolised, is stored in adipose and muscle tissues.

Metabolism and Excretion

The liver and kidney are the main sites for the metabolic activation of vitamin D3. Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Colecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life of weeks to months. Metabolites are eliminated primarily (96%) through the bile and faeces.

IV.3 Pharmacodynamics

Vitamin D is an important nutrient in the maintenance of bone health. The primary functions of vitamin D are the regulation of intestinal calcium absorption and the stimulation of bone resorption leading to the maintenance of serum calcium concentration.

IV.4 Clinical Efficacy

Clinical symptoms of vitamin D deficiency manifest as rickets in children and osteomalacia in adults.

For vitamin D deficiency prevention in adults and the elderly with an identified risk, daily doses of 800 – 1600 IU of vitamin D3 daily have been systematically investigated in clinical studies. Similar doses are well established in authorised product SmPCs. In adolescents, a dose of 800 IU has been supported for this indication.

For the adult and elderly populations with osteoporosis and therefore at risk of vitamin D deficiency, a dose of 800 – 1600 IU/day (up to a maximum dose of 2000 IU/day) is fully supported.

For the treatment of Vitamin D deficiency in adults and the elderly, daily doses of 800 – 4000 IU of vitamin D3 have been investigated in clinical studies. Similar doses are well established in the treatment of vitamin D deficiency as seen in the SmPCs of several authorised products and so this dose is considered to be acceptable in these populations. In adolescents, a dose of 800 – 1600 IU (up to a maximum daily dose of 2000 IU) has been supported for this indication.

IV.5 Clinical Safety

The Applicant has given an adequate overview of the safety profile of colecalciferol which is well established. Undesirable effects reported with use include:
Hypersensitivity reactions, hypercalcaemia and hypercalciuria, pruritus, rash and urticarial.
The SmPC and PL contain the relevant safety warnings and are generally in line with other licensed colecalciferol products.

Risk Management Plan

The applicant 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 Colecalciferol EQL Pharma 800 IU and 2000 IU tablets.
The revised risk management plan (version 0.3, signed 10/11/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	• None
Important potential risks	• None
Missing Information	• None

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

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 overall assessment outcome of Colecalciferol EQL Pharma 800 IU Tablet and Colecalciferol EQL Pharma 2000 IU Tablet from EQL Pharma AB, is positive.

The MAH 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 EQL Pharma 800 IU Tablet and Colecalciferol EQL Pharma 2000 IU Tablet demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

13.04.2026