IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Solferol 20,000 IU Soft Capsules
Colecalciferol
PA23126/002/001

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 Vitamin D_3 20,000 IU Capsules, from Alissa Healthcare Research Limited on 14 October 2016 indicated for:

· the prevention and treatment of vitamin D deficiency.
· as an adjunct to specific therapy for osteoporosis in patients at risk of vitamin D insufficiency or with vitamin D deficiency.

Vitamin D_3 20,000 IU Capsules is indicated 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 a well-established use application. The RMS is IE, with the UK 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: Vitamin D3 20,000 IU Capsules
Name(s) of the active substance(s) (INN): COLECALCIFEROL
Pharmacotherapeutic classification (ATC code): A11CC05 Vitamin D and analogues
Pharmaceutical form and strength(s): Capsule 20,000 International Unit
Marketing Authorisation Number(s) in Ireland (PA): PA1887/002/001
Marketing Authorisation Holder: Alissa Healthcare Research Limited
MRP/DCP No.: IE/H/443/001/DC
Reference Member State: IE
Concerned Member State: UK (Northern Ireland)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Vitamin D3 20,000 IU Capsules, soft.

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 Vitamin D3 20,000 IU Capsules, soft.

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. This is a well-established use application as Vitamin D3 has been in well-established use within the European Union for more than ten years, demonstrating a recognized efficacy and safety. A non-clinical overview has been provided and written by an appropriately qualified person. This is satisfactory.

III.2 Pharmacology

Vitamin D3 has an important role in bone metabolism in maintaining levels of calcium and phosphorous. Activation of vitamin D receptor (VDR) by 1,25- dihydroxycolecalciferol (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, and does not indicate any risk with respect to general toxicity, genotoxicity, carcinogenicity or reproductive and developmental toxicity.

III.5 Ecotoxicity/environmental risk assessment

In line with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00), an ERA is not required for Vitamins since they are unlikely to result in significant risk to the environment. The absence of an environmental risk assessment is thus considered acceptable.

III.6 Discussion on the non-clinical aspects

Vitamin D3 20,000 IU Capsules are a generic proprietary medicinal product. Vitamin D3 has been in well-established use within the European Union for more than 10 years, demonstrating a recognized efficacy and safety. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. No new non-clinical studies were submitted. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate.

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

IV.2 Pharmacokinetics

The applicantprovided 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 gets 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

<u>Prevention of vitamin D deficiency</u>

The applicant's summary of the available data on the prevention of vitamin D deficiency is considered adequate. According to the UK Endocrine Society's Clinical Guidelines, the recommended daily allowance (RDA) for adults aged 19-70 years is 600IU/day and for those aged 70 years, 800IU/day. A patient's dietary intake of vitamin D intake should also be taken into account. A dose of 20,000 IU per month works out at approximately 714 IU/day (assuming a month is 28 days). The SmPC allows for higher dosing if required and dosing of patients will be under medical supervision and monitoring.

Treatment of vitamin D deficiency:
The applicant's summary of the available data in high dose vitamin D treatment for deficiency is considered adequate. The summary contains a number of studies with doses and posologies similar to that requested. The posology for the treatment of vitamin D deficiency states is in line with the UK National Osteoporosis Society guidelines 2013 and other similar licensed products and is considered acceptable.

As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency
The indication for use as an adjunct in the treatment of osteoporosis is considered to be adequately supported. The studies presented show that the use of intermittent high dose vitamin D formulations is effective as an adjunct to specific treatments for osteoporosis. The SmPC allows for higher dosing if required and dosing of patients will be under medical supervision and monitoring.

The Applicant has adequately supported the proposed indications and posology. The Summary of Product Characteristics (SmPC) and Patient Leaflet (PL) are generally in line with approved medicinal colecalciferol products in the United Kingdom and Ireland and are considered acceptable.

IV.5 Clinical Safety

Based on the clinical studies provided by the applicant, the safety of the capsules containing 20,000 IU 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.

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 Vitamin D3 20,000 IU Capsules (Colecalciferol).(Revised RMP Version 1.2 is acceptable (date of final sign off 19/1/2/2015))

- Summary table of safety concerns as approved in RMP

Important identified risks	Important potential risks	Missing information
· Hypersensitivity to the active substance or to any of the excipients · Hypercalcaemia and / or hypercalciuria · Hypervitaminosis D · Nephrolithiasis · Lack of efficacy due to severe renal impairment	Drug Interactions, such as digitalis and other cardiac glycosides or diuretics Use in sarcoidosis or other granulomatous disorders	None

- Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/approved in RMP

Safety Concern
Important Identified Risks
Hypersensitivity to the active substance or to any of the excipients
Hypercalcemia and / or hypercalciuria
Hypervitaminosis D
Nephrolithiasis
Lack of efficacy due to severe renal impairment
Important Potential Risks

Drug Interactions, such as digitalis and other cardiac glycosides or diuretics
Use in sarcoidosis or other granulomatous disorders

Missing Information

Routine Risk Minimisation Measures	**Additional Risk Minimisation Measures**
Proposed SPC Section 4.3 'Contraindications' states: Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SPC.	None proposed
Proposed SPC Section 4.3 'Contraindications' states: Diseases or conditions resulting in hypercalcaemia and / or hypercalciuria	None proposed
Proposed SPC Section 4.3 'Contraindications' states: Hypervitaminosis D	None proposed
Proposed SPC Section 4.3 'Contraindications' states: Nephrolithiasis.	None proposed
Proposed SPC Section 4.3 'Contraindications' states: Severe renal impairment. Proposed SPC Section 4.4 'Special warnings and precautions for use' states: Vitamin D3 20,000 IU Capsules should be used **with caution** in patients with impaired renal function, impaired renal calcium and phosphate excretion, a tendency to form kidney stones (calculi), treatment	None proposed

with benzothiadiazine derivatives and in immobilized patients with caution (risk of hypercalcaemia, hypercalciuria). In these patients, the calcium levels in plasma and urine are monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used (see section 4.3, contraindications).	

Proposed SPC Section 4.4 'Special warnings and precautions', SPC Section 4.5 'Interaction with other medicinal products and other forms of interaction' states: Caution is required in patients receiving treatment for cardiovascular disease (see Section 4.5 – cardiac glycosides including digitalis) or diuretics. Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation. Concomitant use of glucocorticoids can decrease the effect of vitamin D. Rifampicin may also reduce the	None proposed

effectiveness of vitamin D3 due to hepatic enzyme induction. Isoniazid may reduce the effectiveness of vitamin D3 due to inhibition of the metabolic activation of vitamin D. Thiazide diuretics may result in hypercalcaemia due to the reduction of the renal calcium excretion.The calcium levels in plasma and urine should be monitored during long-term therapy. Vitamin D3 might increase the intestinal absorption of aluminum. The toxicity effects of digitalis and other cardiac glycosides may be accentuated (risk of cardiac arrhythmias) with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium levels in plasma and urine. Simultaneous treatment with ion exchange resins such as cholestyramine, colestipol hydrochloride, orlistat or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. The cytotoxic agent actinomycin and imidazole antifungal agents interfere with	

vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.	
Proposed SPC Section 4.4 'Special warnings and precautions for use' states: The active metabolite of vitamin D3 (1, 25-dihydroxycholecalciferol) may affect the phosphate balance. Therefore, in conditions with increased phosphate levels, treatment with a phosphate binder may be considered. Caution should be taken in patients who are suffering from sarcoidosis or other granulomatous disorders because of the risk of increased conversion of vitamin D to its active metabolite. These patients should be monitored with regard to the calcium content in serum and urine.	None proposed
None	

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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

Beneficial effects:
The applicant has adequately supported the proposed indications and posology in adult patients:
Prevention of vitamin D deficiency
According to the UK Endocrine Society's Clinical Guidelines, the RDA for adults aged 19-70 years is 600IU/day and for those aged 70 years, 800IU/day. A patient's dietary intake of vitamin D intake should also be taken into account. A dose of 20000IU per month works out at circa 714 IU/day (assuming a month is 28 days). The SmPC allows for higher dosing if required and dosing of patients will be under medical supervision and monitoring. The proposed posology is therefore considered acceptable.
Treatment of vitamin D deficiency:
The applicant's summary of the available data in high dose vitamin D treatment for deficiency is considered adequate. The summary contains a number of studies with doses and posologies similar to that requested. The posology for the treatment of vitamin D deficiency states is in line with the UK National Osteoporosis Society guidelines 2013 and other similar licensed products and is considered acceptable.
As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency
The use as an adjunct in the treatment of osteoporosis is considered supported. The studies presented show that the use of intermittent high dose vitamin D formulations is effective as an adjunct to specific treatments for osteoporosis. The SmPC allows for higher dosing if required and dosing of patients will be under medical supervision and monitoring. The proposed posology is therefore considered acceptable.

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 Vitamin D_3 20,000 IU Capsules 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 Vitamin D_3 20,000 IU Capsules demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable.

VI. REVISION DATE

February 2021

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval

CRN00C139 MA Transfer	SPC section 7, 8 Package Leaflet New MA Holder: Windzor Pharma Ireland Limited, The Office Suite, Unit 2 Holywell Commercial Centre, Swords, Co Dublin, Ireland New MA number: PA23126/002/001	26/02/2021	26/02/2021	Approved