IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Solferol 400 IU Soft Capsules
Colecalciferol
PA23126/001/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Vitamin D3 400, 800, 1000 and 10000 IU Capsules, soft, from Alissa Healthcare Research Limited on 6th October 2017.

400 IU
Prevention of Vitamin D deficiency in pregnant and breastfeeding women with an identified risk. Vitamin D3 Capsules is indicated in adults and adolescents.

800,1000 & 10000 IU
Treatment of Vitamin D deficiency.
Prevention of Vitamin D deficiency in high-risk patients.
As an adjunct to specific therapy for osteoporosis in patients with Vitamin D deficiency or at risk of Vitamin D insufficiency.
Vitamin D3 Capsules are indicated in adults, the elderly and adolescents.

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, and the UK is the sole CMS.

In the RMS, the 400 IU strength is not subject to medical prescription and may be supplied through pharmacies only.

In the RMS, the 800, 1000 and 10000 IU strengths are prescription-only medicines which may be supplied through pharmacies only.

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

Name of the product: Vitamin D3 400, 800, 1000 and 10000 IU Capsules, soft
Name(s) of the active substance(s) (INN): COLECALCIFEROL
Pharmacotherapeutic classification (ATC code): A11CC05 Vitamin D and analogues
Pharmaceutical form and strength(s): 400, 800, 1000 and 10000 IU Capsules Soft
Marketing Authorisation Number(s) in Ireland (PA): PA1887/008/001-004
Marketing Authorisation Holder: Alissa Healthcare Research Limited
MRP/DCP No. : IE/H/444/001-004/DC
Reference Member State: IE
Concerned Member State: UK (Northern Ireland)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Vitamin D3 400, 800, 1000 and 10000 IU Capsules, soft.

II.2 Drug substance

The active substance is colecalciferol (INN term) / cholecalciferol (Ph. Eur. term), 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.

II.3 Medicinal product

P.1 Composition

Each 400 IU capsule contains colecalciferol, equivalent to 10 micrograms Vitamin D_3.
Each 800 IU capsule contains 800 IU of colecalciferol, equivalent to 20 micrograms Vitamin D_3.
Each 1,000 IU capsule contains 1,000 IU of colecalciferol, equivalent to 25 micrograms Vitamin D_3.
Each 10,000 IU capsule contains 10,000 IU of colecalciferol, equivalent to 250 micrograms Vitamin D_3.

The excipients in the medicinal product are listed in section 6.1 of the SmPCs.
A visual description of the product is included in section 3 of the SmPCs.

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 suitably qualified manufacturing sites.

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 Ph. Eur. or are adequately controlled by the manufacturer's specifications.

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 SmPCs.

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 400, 800, 1000 and 10000 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, 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 $PEC_{surfacewater}$ is 0.00135µg/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, also known as cholecalciferol and vitamin D_3, is a well-known active substance with established efficacy and tolerability. Colecalciferol is produced naturally in the skin by conversion of 7-dehydrocholesterol to colecalciferol by ultraviolet light radiation from the sun. In the absence of adequate sunlight exposure, colecalciferol is an essential dietary nutrient. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults.

IV.2 Pharmacokinetics

The applicant provided an adequate overview of the pharmacokinetics of colecalciferol.

Colecalciferol is absorbed through the small intestine in the presence of bile acids and gets into the blood through lymphatic circulation.

Colecalciferol is converted to 25-hydroxycolecalciferol in the liver, and stored until needed.

Conversion to the active calcium-mobilizing hormone 1,25-dihydroxy colecalciferol (calcitriol) in the kidney is tightly regulated.

Vitamin D and its metabolites are excreted in faeces and urine.

IV.3 Pharmacodynamics

The pharmacodynamics of colecalciferol has been adequately discussed by the applicant and has been based on published literature.

Vitamin D increases the intestinal absorption of calcium, increases the calcium reabsorption in the kidneys and bone formation, and decreases the level of parathyroid hormone (PTH).

IV.4 Clinical Efficacy

The applicant's summary of the available data on the proposed indications and posology is considered adequate.
The indications are as follows:

<u>400 IU</u>
Prevention of Vitamin D deficiency in pregnant and breastfeeding women with an identified risk. Vitamin D3 Capsules is indicated in adults and adolescents.

<u>800,1000 & 10000 IU</u>
Treatment of Vitamin D deficiency.
Prevention of Vitamin D deficiency in high-risk patients.
As an adjunct to specific therapy for osteoporosis in patients with Vitamin D deficiency or at risk of Vitamin D insufficiency.
Vitamin D3 Capsules are indicated in adults, the elderly and adolescents.

The posologies are as follows:

400 IU

Adults and adolescents

Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation.

Pregnancy and breast-feeding

- Prevention of deficiency: The usual dose is 400 IU/day (1 capsule)

Before starting the vitamin D therapy, the patient's dietary habits should be carefully evaluated by the doctor and artificially added vitamin D content of certain food types should be taken into consideration.

Certain populations are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D:

- Breast-feeding women who choose not to give the infant a vitamin D3 supplement.
- Institutionalised or hospitalised individuals
- Dark skinned individuals
- Individuals with limited effective sun exposure due to protective clothing or consistent use of sun screens
- Obese individuals
- Patients being evaluated for osteoporosis
- Use of certain concomitant medications (e.g., anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease
- Those recently treated for vitamin D deficiency, and requiring maintenance therapy.

Paediatric population

Vitamin D3 Capsules should not be used in children under 12 years.

Method of administration

Oral

The capsules should be swallowed whole (not chewed) with water.

800,1000 & 10000 IU

Adults

Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation. Vitamin D_3 800 IU and 1,000 IU capsules are suitable for daily vitamin D supplementation, while the 10,000 IU dose is suitable for weekly vitamin D dosing (equivalent to 1,400 IU/day) respectively, which should be taken into consideration and dosage should be established by a physician.

Osteoporosis: For the adjunct therapy of osteoporosis a daily dose of 800-1,000 IU is recommended. Daily doses equivalent to 2,000 IU vitamin D should be considered in fragile elderly patients who are at particular risk of falls and fractures. Patients should receive supplemental calcium if intake from diet is inadequate.

Vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults and the elderly: 800 IU-4,000 IU daily for up to 12 weeks depending upon the severity of the disease and the patient`s response to treatment.

Vitamin D insufficiency (serum levels 25-50 nmol/l or 10-20 ng/ml) in adults and the elderly:

AND

Long term maintenance therapy following treatment of deficiency in adults and the elderly:

AND

Prevention of vitamin D deficiency:

800-1600 IU daily.

Vitamin D deficiency or insufficiency in adolescents 12-18 years: 800 IU daily depending on the severity of the disease and the patient`s response to treatment. Should only be given under medical supervision.

Hepatic impairment: No dose adjustment is necessary for patients with hepatic impairment.

During vitamin D therapy, calcium and phosphor intake has fundamental significance with respect to the success of the treatment.

Before starting the vitamin D therapy, the patient's dietary habits should be carefully evaluated by the doctor and artificially added vitamin D content of certain food types should be taken into consideration.

Certain populations are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D:
- Institutionalised or hospitalised individuals
- Dark skinned individuals
- Individuals with limited effective sun exposure due to protective clothing or consistent use of sun screens
- Obese individuals
- Patients being evaluated for osteoporosis
- Use of certain concomitant medications (e.g., anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease
- Those recently treated for vitamin D deficiency, and requiring maintenance therapy.

Medical supervision is required as dose response may vary dependent on patient response (see section 4.4).

Paediatric population
Vitamin D_3 Capsules should not be used in children under 12 years.

Method of administration
Oral
The capsules should be swallowed whole (not chewed) with water.

The indications and posology in the SmPCs are in line with other similar licensed products and are considered to be acceptable.

IV.5 Clinical Safety

Based on the clinical studies provided by the applicant, the safety of the capsules containing 400, 800, 1000 and 10000 IU of colecalciferol is considered well-established. The applicant has given an adequate overview of the safety of colecalciferol. The SmPC and Patient Leaflet (PL) contain the relevant safety warnings and are generally in line with other licensed colecalciferol products. Undesirable effects listed in the SmPC are:

Immune system disorders:
Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angio-oedema or laryngeal oedema.

Metabolism and nutrition disorders:
Uncommon: hypercalcaemia and hypercalciuria.

Skin and subcutaneous disorders:
Rare: Pruritus, rash and urticaria.

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.

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 Colecalciferol. RMP version 1.2 is acceptable (dated 23/10.2013). The proposed summary of safety concerns is acceptable. Routine pharmacovigilance activities are recommended. No additional pharmacovigilance activities or additional risk minimisation measures are considered necessary.

Safety Specification
Important identified risks:
1. Hypersensitivity to the active substance or to any of the excipients
2. Hypercalcaemia and/or hypercalciuria
3. Hypervitaminosis D
4. Nephrolithiasis
5. Lack of efficacy due to severe renal impairment

Important potential risks:
1. Drug interactions, such as digitalis and other cardiac glycosides or diuretics
2. Use in sarcoidosis or other granulomatous disorders

Important missing information:
None

• 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.

IV.6 Discussion on the clinical aspects

Beneficial effects:
The applicant has adequately supported the proposed indications and posology.

Undesirable effects:
The following undesirable effects are mentioned in the proposed SmPCs and are similar to other approved colecalciferol products: hypercalcaemia, hypercalciuria, pruritus, rash, urticarial and hypersensitivity reactions.

Acute or chronic overdose of vitamin D can cause hypercalcaemia. Symptoms of hypercalcemia are anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, confusion, polydipsia, polyuria, bone pain, calcification in the kidneys, kidney stones, vertigo, and cardiac arrhythmia in severe cases. Hypercalcaemia in extreme cases may lead to coma or even death. Persistently high levels of calcium may cause irreversible renal impairment and soft tissue calcification.

Conclusion:
The overall assessment outcome of Vitamin D3 400, 800, 1000 and 10000 IU Capsules, soft is positive.

V. OVERALL CONCLUSIONS

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 Vitamin D3 400, 800, 1000 and 10000 IU Capsules, soft 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

February 2021

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN00C135 MA Transfer	SPC section 7, 8 Package Leaflet	26/02/2021	26/02/2021	Approved

	New MA Holder: Windzor Pharma Ireland Limited, The Office Suite, Unit 2 Holywell Commercial Centre, Swords, Co Dublin, Ireland New MA number: PA23126/001/001-004			