IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Egostar 22400 IU film-coated tablets
Cholecalciferol concentrate
PA23312/001/001

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Egostar 22400 IU film-coated tablets, from Jaba Recordati, S. A. on 8th April 2022 for the following indications:

Prevention of vitamin D deficiency in patients with an identified risk.
Initial treatment of clinically relevant vitamin D deficiency.
As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.
Egostar is indicated in adults.

This application for a marketing authorisation was submitted as a new national procedure application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application.

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	Egostar 22400 IU film-coated tablets
Name(s) of the active substance(s) (INN)	Cholecalciferol concentrate
Pharmacotherapeutic classification (ATC code)	A11CC05-colecalciferol
Pharmaceutical form and strength(s)	22400 international unit(s)
Marketing Authorisation Number(s) in Ireland (PA)	PA22948/001/001
Marketing Authorisation Holder	Jaba Recordati, S. A., Av. Jacques Delors, Ed. Inovação 1.2, Piso 0 - Taguspark 2740-122 Porto Salvo , Portugal
Case No.	CRN0093KN

II. QUALITY ASPECTS

II.1. Introduction

This application is for Egostar 22400 IU film-coated tablets.

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.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet of Egostar contains 560 micrograms (22 400 IU) of cholecalciferol (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 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 the dosage form, 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(s) 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 Egostar 22 400 IU Film coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application is based on well-established clinical use.

Pharmacodynamic, pharmacokinetic and toxicological properties of cholecalciferol are well known. As cholecalciferol is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 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. Furthermore, cholecalciferol is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, cholecalciferol is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

As cholecalciferol is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. There are no objections to approval of Egostar 22400 IU film-coated tablets from a non-clinical point of view.

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 an established efficacy and safety profile.

IV.2 Pharmacokinetics

Vitamin D is a group of fat-soluble prohormones with the two major biologically inert precursors being vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol).

Vitamin D3 is almost completely absorbed from the gastro-intestinal tract after oral administration, if the lipid absorption is normal.

In plasma, vitamin D3 is transported to the liver via binding protein vitamin D, where the first hydroxylation occurs. The concentration of circulating 25(OH)D (calcidiol) are an indicator of vitamin D state.

25(OH)D undergoes hydroxylation in the kidney to form 1,25(OH)D (calcitriol).
Cholecalciferol and its metabolites can be stored in the muscle and fat tissues during several months.

Calcitriol undergoes further hydroxylations before being eliminated. The primary route of elimination of vitamin D and its hydroxylated derivatives and sulfates is through the bile with about 2% excreted in the urine.

IV.3 Pharmacodynamics

Cholecalciferol (vitamin D3) is important for calcium homeostasis and for optimal skeletal health. Its major function is to increase the efficiency of calcium absorption from the small intestines. Vitamin D also enhances the absorption of phosphorus from the distal small bowel. Adequate calcium and phosphorus absorption from the intestine is important for proper mineralisation of the bone. The second major function of vitamin D is involvement in the maturation of osteoclasts, which resorb calcium from the bones.

IV.4 Clinical Efficacy

The applicant has provided several appropriate literature references demonstrating that the efficacy of cholecalciferol is well established in the proposed indications.

IV.5 Clinical Safety

The applicant has provided several appropriate literature references demonstrating that the safety of cholecalciferol is well established. Undesirable effects listed in the SmPC are:
Metabolism and nutrition disorders
Uncommon: Hypercalcaemia and hypercalciuria.
Skin and subcutaneous disorders
Rare: Pruritus, rash and urticaria.
Long-term treatment
In case of hypercalcemia, or renal function impairment signals the dose should be reduced or the treatment discontinued.

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

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 Egostar 22400 IU film-coated tablets.
The revised RMP (version 0.4, dated 07/01/2020) 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

The clinical aspects of this medicinal product are well established and acceptable.

V. OVERALL CONCLUSIONS

Egostar 22400 IU film-coated tablets has a proven chemical-pharmaceutical quality and a well-established and favourable efficacy and safety profile. The applicant has appropriately demonstrated this profile using appropriate bibliographic references.

From a quality perspective the overall assessment outcome of Egostar 22400 IU film-coated tablets 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 Egostar 22400 IU film-coated tablets has 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

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