LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Divisun
(colecalciferol)

SE/H/1122/02-04/DC

This module reflects the scientific discussion for the approval of Divisun. The procedure was finalised on 2015-10-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Divisun, 1000 IU, 2000 IU and 4000 IU, tablet, is a well-established use application made according to Article 10a of Directive 2001/83/EC. The applicant, Meda AB applies through the Decentralised Procedure. The active substance cholecalciferol is the same as in Divisun, tablets, marketed by Meda AB since 2012.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of vitamin D is well-known and text-book knowledge. Products containing vitamin D have been available in the EU for more than 20 years and their use is well-established with recognised efficacy and acceptable

safety. The non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology is adequate. No further studies are required and the applicant provides none.

No clear toxic level has been defined for vitamin D. However, upper levels of intake have been proposed by EFSA (European Food Safety Authority) in 2012 which the applicant refers to.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) is not required for Vitamins since they are unlikely to result in significant risk to the environment. Divisun is thus not considered to pose any risk to the environment.

III.3 Discussion on the non-clinical aspects

This application for Divisun is based on well-established use. No new non-clinical studies are therefore required and the applicant provides none. A non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology based on a review of published literature has been provided and is considered to be adequate.

There are no objections to the approval of this project from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is an application based on well-established medicinal use for more than 10 years in the community and in accordance with Article 10a of Directive 2001/83/EC clinical trials are replaced by scientific literature.

IV.2 Pharmacokinetics

No new pharmacokinetic studies have been conducted and none are needed for this extension application. Due to the nature of the active substance, it is not considered necessary to compare the bioavailability of vitamin D from the new applied strengths with the previously approved strength of Divisun (800 IU) or with other existing vitamin D containing products on the market. In addition the applied higher strengths of Divisun (1000 IU, 2000 IU and 4000 IU) have the same qualitative composition as the previously approved Divisun 800 IU and the composition is quantitatively proportional within all strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been conducted and none are needed for this extension application.

IV.4 Clinical efficacy

Vitamin D deficiency can cause rachitis and osteomalacia and contributes, with other factors, to osteoporosis, falls and frailty in the elderly.Vitamin D has numerous functions within the body, but evidence between supplementation and health benefit beyond bone health are lacking despite a large number of observational studies and meta-analyses. Data presented and several guidelines and recommendations support the combined use of vitamin D and Ca as a first-line strategy for the treatment of osteoporosis in patients who are at risk of vitamin D deficiency. However, most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent.
Despite a continuing paucity of data for a higher vitamin D intake, the EFSA set the upper level for adults including pregnant and lactating women as well as for children and adolescents to 4,000 IU/d.

Vitamin D deficiency is defined as serum levels of 25-hydroxycolecalciferol (25(OH)D) <25 nmol/l. Higher doses of 2,000-4,000 IU may be needed in some patient groups to treat vitamin D deficiency.

IV.5 Clinical safety

Hypersensitivity to vitamin D can occur, including anaphylactic reactions. Some patients with sarcoidosis, tuberculosis, or lymphoma become hypercalcaemic in response to any increase in vitamin D nutrition. For these patients, dietary or supplemental sources of vitamin D should be avoided.
The symptoms of chronic hypervitaminosis D are connected with the physiological consequences of hypercalcaemia, which occur once the Ca elimination capacity of the kidneys is exceeded. The most frequently noted clinical manifestations of hypervitaminosis D are anorexia, weight loss, weakness, fatigue, disorientation, vomiting, and constipation. Excessive intake of vitamin D is linked to the development of hypercalcaemia and its associated effects including hypercalciuria, ectopic calcification, and renal and cardiovascular damage.

IV.6 Risk Management Plans

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 Divisun.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	*Hypercalcaemia (increased levels of calcium in the blood), hypercalciuria (increased levels of calcium in the urine)* *Allergic (hypersensitive) reactions*
Important potential risks	*Vitamin D toxicity*
Missing information	*Use in children* *Use in patients with severe renal impairment*

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

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

Important identified risks		
Risk	What is known	Preventability
Hypercalcaemia (increased levels of calcium in the blood), hypercalciuria (increased levels of calcium in the urine).	Vitamin D increases the gastrointestinal uptake of calcium. Vitamin D should therefore be used with caution in patients with conditions known to have an increased risk of metabolism of vitamin D into its active form. Vitamin D should be used with caution in patients with impairment of renal function.	Follow the recommendation provided in the product information which states that Vitamin D_3 should not be used in patients with kidney problems or a history of kidney stones.
Allergic (hypersensitive) reactions	The frequency of hypersensitivity reactions cannot be estimated.	Follow the recommendations given in the product information that colecalciferol should not be used by patients allergic to colecalciferol or any of the other ingredients of Divisun/Colecalciferol Meda.

Important potential risks	
Risk	What is known
Vitamin D toxicity	Excessive dosing over long periods of time may constitute a risk. In man toxicity has not been reported at doses lower than 10.000 IU per day. With the maximum daily dosage 4000 IU there is a great safety margin to doses with a potential to cause toxicity.
Missing information	Use in children has not been studied. Use in patients with severe renal impairment has not been studied.

The RMP is approved.

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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Divisun (former Desunin) 800 IU, tablets, in regulatory procedure SE/H/1122/01/DC. The content of the PL for the new strengths is almost identical to the PL for 800 mg tablets. In the above procedure bridging was used. Two 'parent' PL were used; where Recikalc-D forte 500 mg/800 IU was used regarding content, and the other parent PL used for style and layout was Relifex 500 mg (approved by MHRA for the submission PL 19166/0060-0009).
As the content of PL for the new strengths is almost identical to the PL for Divisun 800 mg tablets and the layout is identical to Divisun 800 IU the bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Beneficial effects:
For the indications of prevention of vitamin D deficiency and supportive treatment in osteoporosis, daily doses above 1000 IU of vitamin D3 daily have not been systematically investigated in clinical studies and should therefore not be recommended.

Higher doses (up to 4000 IU daily) may be necessary in the treatment of vitamin D deficiency, defined as serum 25-hydroxycalciferol (25OHD) <25 nmol/l. In these cases, the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.

Undesirable effects:
The following adverse events are mentioned in the SmPC for approved D-vitamin products: hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea, and hypersensitivity reactions such as pruritus, rash, urticaria.
Toxicity reported from vitamin D supplementation is rare. Toxicity manifests as hypercalcemia and hypercalciuria, leading to renal failure as a results of nephrocalcinosis and nephrolithiasis and neurologic symptoms including coma. Excessive vitamin D intake is associated with additional adverse events, including pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting and weight loss. These are all due to hypercalcaemia.

Conclusion:
The benefit/risk ratio is considered positive and Divisun, 1000 IU, 2000 IU and 4000 IU tablets for the approved indications.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
Variation will be submitted to harmonize Divisun 800 IU tablets (SE/H/1122/01/DC) dossier to that of Divisun 1000 IU tablets (SE/H/1122/02/DC).	April 2016
To perform a stressed stability study to further confirm the stability indicating capability of the HPLC in-house assay method. The study will be finalized during 2015 and report will be available no later than January 2016. Should the outcome of the study necessitate a variation it will be submitted no later than April 2016.	January 2016

To further address and discuss the outstanding point from MHRA: A limit for related substances in line with the requirements of the relevant guideline along with a valid method of analysis should be added to the specification. Any applicable variation will be submitted no later than April 2016.	April 2016

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Divisun, 1000 IU, 2000 IU and 4000 IU, tablet, was positively finalised on 2015-10-22.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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