LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Divisun
(cholecalciferol)

SE/H/1122/01/DC

This module reflects the scientific discussion for the approval of Divisun. The procedure was finalised 2012-04-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Meda AB has applied for a marketing authorisation for Divisun, tablets, 800 IU (20 microgram). The active substance is cholecalciferol. Vitamin D increases the intestinal absorption of calcium and phosphate. Administration of vitamin D3 counteracts development of rickets in children and osteomalacia in adults. It also counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which causes increased bone resorption. In addition to bone and intestinal mucosa many other tissues have vitamin D receptors, to which the active hormonal form of vitamin D, calcitriol, bind and modulate a great amount of genes. Vitamin D modulates the innate and the adaptive immune system. Vitamin D prevents and may heal the vitamin D deficiency-related myopathy and muscle dysfunction and reduces fall frequency in elderly people.
For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Divisun is presented in the form of tablets containing 800 IU of colecalciferol which corresponds to 20 microgram vitamin D_3. . The excipients are pregelatinzed maize starch, isomalt (E 953), magnesium stearate, sucrose, sodium ascorbate, triglycerides, medium chain, silica, colloidal anhydrous, sodium starch octenyl succinate (E 1450) and all-rac-alpha-tocopherol. The tablets are packed in PVC/PVDC/aluminium blisters or HDPE plastic containers.

II.2 Drug Substance

Colecalciferol has a monograph in the Ph Eur.

The structure of colecalciferol has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Divisun tablets is formulated using excipients described in the current Ph Eur..All raw materials used in the product are of non-animal origin and have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, whit the storage instructions; do not store above 25ºC. Store the tablets in the original container, in order to protect from light. Keep the container tightly closed in order to protect from moisture.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Colecalciferol/vitamin D_3 is a well-known substance for which pharmacodynamic, pharmacokinetic and toxicological properties are well-known and text-book knowledge. Products containing vitamin D_3 have been available in the EU for more than 20 years. The recomended dose level for Divisun tablet (800 IU, equivalent to 20 µg vitamin D_3) is within the dosage range commonly used in clinical practise and below the upper level of intake proposed by the EU Scientific Committee on Food in 2002 (50µg/day for adolescents and adults) and Food and Nutrition Board, Institute of Medicine of the National Academies, US in 2010 (4000IU/day for adults and children ≥ 9 years old).

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

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. The absence of an environmental risk assessment is thus considered acceptable.

III.3 Discussion on the non-clinical aspects

In conclusion, the applicant has presented an adequate nonclinical evaluation of the product. Divisun can therefore be recommended for approval from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 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 D_3, 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.

IV.2 Clinical efficacy

The Applicant has in some detail described the increments obtained with different doses of 25(OH)D seen in different studies. The data could be summarised as follows: The mean increment in 25(OH)D per given microgram cholecalciferol varies between 0.58 and 3.50 nmol/L in different studies.

A daily dose of 10 microgram seems to be insufficient for a considerable number of patients, while 20 microgram more efficiently results in a 25(OH)D level above 50 nmol/L in most but not all subjects. For attaining a level above 75 nmol/L, a daily dose of 50 microgram or more may be necessary. A follow-up assessment of serum 25(OH)D during supplementation should be considered after starting supplementation with vitamin D.

Supplementation with vitamin D and calcium has been convincingly demonstrated to reduce the incidence of skeletal fractures in elderly women. Supplementation has early on also been found to be clinically effective in osteomalacia due to vitamin D deficiency.

IV.3 Clinical safety

The safety of cholecalciferol in the dose proposed for the population targeted is considered to be sufficiently well documented by performed clinical studies and by long-standing clinical experience.

IV.4 Discussion on the clinical aspects

The efficacy and safety of cholecalciferol in the proposed doses in target population with vitamin D deficiency/insufficiency is considered to be sufficiently well characterised by the published clinical study data compiled by the Applicant and by the long-standing clinical experience.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 .

In the day 120 report the applicant was requested to clarify why other evidences than those indicated in the day 106 response were submitted.

In the day 180 report the applicant states that regrettably the wrong evidence for bridging to Recikalc-D forte 500mg/800 IU Chewable tablets was submitted at Day 106. The correct reference number for evidence of bridging should be SE/H/805/02/DC as stated in the Final Assessment Report at Day 270.
For Relifex, the MHRA approval letter submitted at Day 106 in this procedure covers all the registered Relifex product formulations in the UK and which were subject of the User Testing submission. Only Relifex Oral Suspension is mentioned in the approval letter, however at the bottom of the document following phrase is seen “This letter refers to Collection ID 69187 and covers the following submissions: PL 19166/0060 – 0009 Leaflet and Final Report” which is the reference number for Relifex 500 mg Tablets.

The clarification was considered as acceptable and the bridging is acceptable. The PL for Divisun is considered as patient friendly.

The risk/benefit ratio is considered positive and Divisun tablets, 800 IU (20 microgram) is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Divisun tablets, 800 IU (20 microgram) was successfully finalised 2012-04-18.

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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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