COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

D-Cura 25.000 IU, 5.600 IU and 12.500 IU, hard capsules (cholecalciferol)

NL/H/6270/001-003/DC

Date: 3 December 2024

This module reflects the scientific discussion for the approval of D-Cura 25.000 IU, 5.600 IU and 12.500 IU, hard capsules. The procedure for D-Cura 25.000 IU, hard capsules was finalised at 13 November 2017 in Germany (DE/H/3387/001/DC). The procedure for D-Cura 5.600 IU and 12.500 IU, hard capsules was finalized at 6 December 2021 in Germany (DE/H/3387/002-003/DC). After a transfer on 22 October 2024, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for D-Cura 25.000 IU, 5.600 IU and 12.500 IU, hard capsules from SMB Laboratoires S.A.

The product is indicated for: Initial treatment of symptomatic vitamin D deficiency in adults.

A comprehensive description of the indications and posology is given in the current SmPC.

The marketing authorisation for D-Cura 25.000 IU, hard capsules has been granted pursuant to Article 10a of Directive 2001/83/EC.
The marketing authorization for D-Cura 5.600 IU and 12.500 IU, hard capsules has been granted pursuant to Article 10a of Directive 2001/83/EC, so called well-established use (WEU) application, as it was a line extension to the already existing marketing authorisation for Decurol 25.000 IU hard capsules (DE/H/3387/001/DC).

II. QUALITY ASPECTS

II.1 Introduction

D-Cura 25.000 IU
D-Cura 25.000 IU is presented in the form of transparent hard gelatin capsule containing 0.625mg cholecalciferol, equivalent to 25.000 IU vitamin D3.
The excipients are: all-rac-alpha-tocopherol acetate, olive oil, refined, gelatin, olive oil, refined and gelatine.
The hard gelatin capsules 25.000 IU are packed into a thermosealed blisters with PVC/aluminium blister packs.

D-Cura 5.600 IU
The finished product is a hard capsule containing 0.14 mg cholecalciferol equivalent to 5.600 IU vitamin D3 packed in PVdc/PE/PVC/ aluminium blister packs.

D-Cura 12.500 IU
The finished product is a hard capsule containing 0.3125 mg cholecalciferol equivalent to 12.500 IU vitamin D3 packed in PVdc/PE/PVC/ aluminium blister packs.

II.2 Drug Substance

D-Cura 25.000 IU
The product contains the active ingredient cholecalciferol which is monographed in Ph. Eur. The drug substance cholecalciferol complies with the current version European pharmacopoeia. The applicant sources the substance from supplier DSM Nutritional Products

Europe Ltd. The manufacturer of the drug substance has obtained a CEP. According to the CEP database, the submitted CEP is the current version.
No re-test period and no information about the container closure system are mentioned in the CEPs.

D-Cura 5.600 IU and 12.5000 IU
As active substance manufacturer, is applied for referring to a CEP granted by the EDQM. A retest has been proven within the CEP.

Manufacturing process
D-Cura 25.000 IU
The control tests and specifications for drug substance product are adequately drawn up. All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacture.

Quality control of drug substance
D-Cura 25.000 IU
An appropriate specification has provided for the active substance Cholecalciferol.
A breakdown of the specification complies with Ph. Eur.-monograph and with additional testing for residual is presented.
Cholecalciferol: The currently valid version CEP has been provided. The additional requirement is: Methyl format not more 1000 ppm as reported in the CEP. In this connection, suitable TSE certificate is provided.
Gelatin: A list of countries and source materials are listed in the Certificate of Suitability. The CEPs are included in section 3.2.R.

Stability of drug substance
D-Cura 25.000 IU
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. For all 3 batches the microbiological tests at the beginning and at the end of the shelf-life should be performed. The applicant confirms that the active substance will be retested before any use.
The proposed retest period of 24 months unopened container at temperature below 5°C could be accepted.

II.3 Medicinal Product

Pharmaceutical development
D-Cura 25.000 IU
The finished product is hard gelatin capsule; 25.000 IU is packed into a thermosealed blisters. The development of the product has been described, the choice of excipients is justified and their functions explained.

D-Cura 5.600 IU and 12.500 IU
The Applicant performed updated development data of the product within the procedure.

Quality control of drug product

D-Cura 25.000 IU

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches.

The applicant confirms that the active substance will be retested before any use that the test of microbial testing to perform for each batch release. Updated release specification of the finished product has been submitted.

D-Cura 5.600 IU and 12.500 IU

The product specifications cover appropriate parameters for the dosage form. Analytical methods and validations of the analytical methods have been presented. Batch analysis has been performed for each strength. The batch analysis results show that the finished product meets the specifications proposed.

Risk assessment according to ICH Q3D and also about nitrosamines is provided. To exclude a risk about nitrosamine contamination the aluminium foil has been changed in regard to overlaquer and printing inks.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up.

Photostability data have also been provided.

The proposed shelf life of 24 months is acceptable. The storage declaration “Do not store above 25°C! Store in the original packaging in order to protect from light and moisture” has been chosen as a precaution and is accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

D-Cura 25.000 IU

In summary, pharmaceutical issues that were raised during the evaluation of the application have been resolved and all the data provided gave the assurance of the quality of the drug product.

The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the proposed quality.

All relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified. The proposed limits are accepted.

The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.

The stability data presently available justifies the claimed shelf-life of two years for the package proposed for marketing.

The control tests and specifications for drug product are adequately drawn up.

D-Cura 5.600 IU and 12.500 IU

The chemical-pharmaceutical documentation and quality overall summary in relation to D-Cura 5.600 IU and 12.500 IU hard capsulesis of sufficient quality in view of the present European regulatory requirements.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Own non-clinical studies have not been performed. The preclinical expert refers to data available in public literature. Cholecalciferol is widely used in the medical practice in Europe to prevent and/or cure vitamin D deficiencies and associated risks. The pharmacology, pharmacokinetics and toxicology are well known and exhibit an established safety profile. Non-clinical aspects are addressed in SmPC and PIL sufficiently.

III.2 Pharmacology

D-Cura 5.600 IU and 12.500 IU
A summary on the effects and actions of vitamin D as well as the consequences of vitamin D deficiencies, based on literature, has been presented. Sufficient discussions on primary, secondary and safety pharmacology and information on possible interactions have been presented.

III.3 Pharmacokinetics

D-Cura 5.600 IU and 12.500 IU
Based on available literature a short summary of data on absorption, distribution and metabolism of vitamin D has been provided. Since pharmacokinetic properties of cholecalciferol are well-known and it has been referred to clinical data, the presented discussion can be regarded as sufficient and no further non-clinical studies on pharmacokinetics are required. Pharmacokinetic interactions reported from non-clinical observations in literature have been summarized and discussed in terms of their clinically relevance.

III.4 Toxicology

D-Cura 5.600 IU and 12.500 IU
Single and repeated dose toxicity have been demonstrated based on published data. Own studies were not conducted by the Applicant and are not required since the available data on the toxicological profile of cholecalciferol are sufficient. Considering a possible overdose, it has been referred to the recommended daily dose by EFSA (European food safety authority). Additionally it has been pointed to the precaution in the SmPC that recommends the check of serum and urinary levels of calcium and creatinine.
The genotoxic potential of the active substance was assessed on available literature data, embracing several in vitro and in vivo tests. None pointed to a mutagenic potential of cholecalciferol or calcitriol, as a metabolite of cholecalciferol.
Own tests on carcinogenicity have not been performed. Since it is an endogenous substance, the provided discussion on available published studies is sufficient to justify the omission of own tests.
Since the effects of vitamin D deficiency on male and female reproduction are well known and animal studies in rats and rabbits on reproduction and development are available, further new

studies are not required. An adequate discussion on the results described in literature was presented. Overdose has to be avoided since a permanent hypercalcemia during pregnancy is related to adverse effects on the developing foetus.
Within the nonclinical overview, the safety of the whole product has to be documented. Thus, an assessment on toxicity of the used excipients is included in the non-clinical overview. Regarding the excipient Tocopherylacetat, it has been referred to the upper limit (UL) of 270 mg/day by scientific committee on food safety.

III.5 Ecotoxicity/environmental risk assessment (ERA)

According to the „Guideline on the environmental risk assessment of medicinal products for human use“, (EMEA/CHMP/SWP/ 4447/00 corr.2) vitamins are exempted from the need to provide new studies on ecotoxicity/environmental risk assessment. The presented justification by the Applicant not to provide such studies is sufficient. It is unlikely that the active substance results in significant risk to the environment also regarding the applied preparation substitutes for the higher strength.

III.6 Discussion on the non-clinical aspects

Since the marketing authorisation has based on article 10a of Directive 2001/83/EC with long standing use and the active substance is well known, there is no need for repetitive preclinical tests on animals or humans.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application was based on Art 10a (bibliographic application). Therefore, only published scientific literature has been reviewed. Pharmacodynamics, pharmacokinetics, efficacy, and safety properties of vitamin D3 are in general well known.
Considering the amount of cholecalciferol contained in the applied medicinal product the initial treatment of symptomatic vitamin D deficiency in adults has been approved as indication.

IV.2 Pharmacokinetics

Pharmacokinetics of cholecalciferol are well known.
All relevant aspects such as influence of food, information for special populations (patients with impaired renal function, impaired hepatic function, obese patients, the paediatric population and the elderly population) and interactions have been addressed in the clinical overview.

In alimentary doses vitamin D is almost completely absorbed from the food together with alimentary lipids. Higher doses are absorbed at a ratio of approx. 2:3. Skin exposed to UV light synthesises vitamin D from 7- dehydrocholesterol. Vitamin D is transferred to the liver via a

specific transport protein. In the liver it is metabolised by a microsomal hydroxylase to 25-hydroxycholecalciferol. Vitamin D and its metabolites are excreted with bile and faeces.

Vitamin D is stored in the fatty tissue and has therefore a long biological half-life. After high vitamin D doses, the 25-hydroxyvitamin D concentrations in the serum may be increased for several months.
Hypercalcaemia due to overdose can persist over several weeks.

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IV.3 Pharmacodynamics

The pharmacodynamics of vitamin D are well known.
Cholecalciferol (vitamin D3) is formed in the skin on exposure to UV light and converted into its biologically active form, 1,25-dihydroxycholecalciferol, in two hydroxylation steps, first in the liver (position 25) and then in the renal tissue (position 1). Along with parathormone and calcitonin, 1,25- dihydroxycholecalciferol has a considerable impact on the regulation of calcium and phosphate metabolism. In vitamin D deficiency the skeleton does not calcify (resulting in rickets) or decalcification of bones occurs (resulting in osteomalacia).

According to production, physiological regulation and mechanism of action, vitamin D3 is to be considered as precursor of a steroid hormone. In addition to physiological production in the skin, cholecalciferol can be supplied via the diet or in the form of a drug. Since in the latter case the product inhibition of cutaneous vitamin D synthesis is circumvented, overdose and intoxications may occur. Ergocalciferol (vitamin D2) is synthesised by plants. Human beings activate it metabolically in the same way as cholecalciferol. It has the same qualitative and quantitative effects.

Adults require 5 µg daily, equivalent to 200 IU. Healthy adults can cover their requirement by producing vitamin D on their own through sufficient exposure to the sun. Alimentary vitamin D supply plays a subordinate role, but can be important under critical conditions (climate, lifestyle).

Fish liver oil and fish are particularly rich in vitamin D; small amounts are found in meat, egg yolk, milk, dairy products and avocado.

Deficiency diseases can occur, among others, in immature pre-term new-born infants, infants exclusively breast-fed for more than six months without calcium-containing foods and children fed a strictly vegetarian diet. The causes of rarely occurring vitamin D deficiency in adults may be inadequate alimentary intake, insufficient exposure to UV light, malabsorption and maldigestion, liver cirrhosis as well as renal insufficiency.

D-Cura 5.600 IU and 12.500 IU
New studies on pharmacodynamics have not been conducted and are not needed for this application.

IV.4 Clinical efficacy

D-Cura 25.000 IU
The medicinal product is indicated for the initial treatment of symptomatic vitamin D deficiency in adults.
The posology is: One capsule (25. 000 IU) weekly.
After first month, lower doses may be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.
Due to the formulation as capsule respectively missing data on posology the administration of D-Cura 25.000 IU is not recommended in the paediatric age group.
In the product information the following contraindications are listed: hypersensitivity to the active substance or to any of the excipients, hypercalcaemia and/or hypercalciuria, nephrolithiasis, serious renal impairment, hypervitaminosis D, and Pseudohypoparathyroidism.
In pregnancy and lactation the high strength formulation is not recommended for treatment.
The use of Vitamin D for the treatment of vitamin D deficiency is widely established. The assessment of clinical data takes into account different national guidelines of treatment in order to harmonize the administration of medicinal products containing vitamin D at high doses within European countries.

D-Cura 5.600 IU and 12.500 IU
In agreement with other decentralized procedures, a weekly dosage of cholecalciferol from 10.000 IU to a maximum of 25.000 IU in the indication 'Initial treatment of symptomatic vitamin D deficiency in adults with a treatment duration of 4 weeks' is accepted. This consensus was reached within recent European decentralised procedures.
For D-Cura 5.600 IU, the posology is given as follows:
Recommended dose: 2-4 capsules weekly (11.200–22.400 IU).
For D-Cura 12.500 IU, the posology is given as follows:
Recommended dose: 1-2 capsules weekly (12.500–25.000 IU).
After the first month, lower doses may be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.

IV.5 Clinical Safety

The overall assessment of safety is based on a substantial time period of well-established use of cholecaciferol. The discussion of the safety aspects in the clinical overview is adequate. A discussion on adverse events has been included. Known side effects of treatment with Vitamin D are hypercalcaemia and hypercalciuria, as well as gastrointestinal (e.g. constipation, flatulence, nausea, abdominal pain, diarrhea) and allergic reactions.
Safety in special populations (paediatric population, patients with renal/hepatic impairment, pregnant and breast-feeding women) has been adequately addressed. This high dosed Vitamin D medicinal product is not recommended in children, adolescents under 18 years of age, pregnant and breast-feeding women.

In the product information, the following contraindications are listed: Hypersensitivity to the active substance or to any of the excipients, hypercalcaemia and/or hypercalciuria, nephrolithiasis, serious renal impairment, hypervitaminosis D, and pseudohypoparathyroidism.
Overdose can lead to hypercalcaemia, hypercalciuria and hypervitaminosis. In the beginning symptoms of overdose are uncharacteristic, in severe cases they may be life-threatening.
In order to avoid overdosing patients at risk have to be excluded from administration, and the duration of treatment is restricted. In patients with an increased risk of hypercalcaemia regular monitoring of serum calcium is needed.
Interactions with other medicinal products are known (e.g. thiazide diuretics, corticosteroids, phenytoin, cardiac glycosides).

IV.6 Risk Management Plan

D-Cura 25.000 IU
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 D-Cura 25.000 IU.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypercalcemia • Hyperphosphatemia • Nephrolithiasis • Nephrocalcinosis • Hypersensitivity
Important potential risks	Off-label use in children younger than 12 years
Missing information	None.

Since the contents of the last submitted RMP version 03 do not appropriately reflect the contents of the last updated product information, the RMP needed to be revised, especially taking into account the fact that the medicinal product under review is not recommended in paediatric patients any more. All parts of the RMP concerning paediatric patients should be revised accordingly. The safety concern 'off-label use in children younger than 12 years' should be replaced by the safety concern 'off-label use in children'.
The future MAH is requested to submit a variation within two months of the finalisation of the marketing authorisation procedure in order to align the contents of the RMP to the contents of the agreed product information.

D-Cura 5.600 IU and 12.500 IU
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 D-Cura 5.600 IU and 12.500 IU.

IV.7 Discussion on the clinical aspects

D-Cura 25.000 IU
Reference is made to relevant published clinical data in order to assess the clinical efficacy and safety of cholecalciferol.
Clinical studies have shown that cholecalciferol is sufficiently effective and safe for the initial treatment of symptomatic vitamin D deficiency in adults. Long-term experience in clinical practice confirms acceptable safe and effective use of preparations containing vitamin D3, if the risk of overdosing is adequately considered.

D-Cura 5.600 IU and 12.500 IU
The clinical overview on clinical pharmacology, efficacy and safety is adequate.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

D-Cura 25.000 IU
The benefit-risk-ratio is considered positive provided that the Product Information (PI) is amended as indicated.

D-Cura 5.600 IU and 12.500 IU
D-Cura 5.600 IU and 12.500 IU are medicinal products with the following indication:
- Initial treatment of symptomatic vitamin D deficiency in adults.

The pharmaceutical quality of D-Cura 5.600 IU and 12.500 IU has been adequately shown and no new non-clinical or clinical concerns have been identified.
The benefit-risk ratio is positive for the intended use.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-