COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

D-CURA 25.000 IU and 100.000 IU, oral solution (cholecalciferol)

NL/H/6464/001-002/DC

Date: 13 August 2025

This module reflects the scientific discussion for the approval of D-CURA 25.000 IU and 100.000 IU, oral solution. The procedure was finalised at 28 August 2012 in Germany (DH/H/2903/001-002/DC). After a transfer on 19 June 2025, the current RMS is the Netherlands. For information on changes after the finalisation 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 and 100.00 IU, oral solution from Laboratoires S.M.B.S.A.

The product is indicated for starting treatment of Vitamin D deficiency in adults.

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

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

D-CURA 25.000 IU and D-CURA 100.000 I.U. are presented in the form of ampoules, oral solution, containing 0.625mg cholecalciferol, equivalent to 25.000 IU vitamin D3.
The oral solutions are clear, slightly yellow, oily liquid with an orange odor.

The excipients are tocopherol acetate; polyglyceryl oleate (E475); olive oil, refined; sweet orange peel oil.

The transparent PVC/PVDC/PE ampoules are packed into packs.

II.2 Drug Substance

The chemical-pharmaceutical documentation and Expert Report in relation to D-CURA ampoules are of sufficient quality in view of the present European regulatory requirements.

The product contains cholecalciferol as active substance. The drug substance cholecalciferol complies with the current version European pharmacopoeia. The Applicant source 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 is mentioned in the CEP.

Quality control of drug substance
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.

Suitable TSE certificate is presented. The CEP has been revised and the currently valid version has been provided. The additional requirement is: Methyl formate not more 1000 ppm as reported in the current CEP.

Certificates of analysis are provided for 3 production batches. The batch size and date of manufacture should be given on the certificates of analysis.

Stability of drug substance
The batches are placed for stability at long term storage conditions at 5°C and 25°C / 60% RH conditions. The stability testing performed for long term at 5°C during 24 months and for accelerates conditions at 25°C/60% RH during 6 months. Additionally, the stability study carried out in accordance to CPMP/QWP/ 122/02, rev 1 corr.
The applicant commits to retest the drug substance before any use.

Approved shelf-life: The proposed retest period of 24 months is justified, when stored in unopened containers and at a temperature of 5ºC +/- 3ºC.

II.3 Medicinal Product

Pharmaceutical development
The finished product is oily liquid, oily liquid filled in PVC/PVDC/PE Ampoule. The composition includes a list of all components of the dosage from, and their amount on a per-unit basis, the function of component and quality standards.

The development of the product has been described, the choice of excipients is justified and their functions explained.

Control of excipients
For the excipients “Polyglyceryl oleate” and “Sweet orange peel oil” have been submitted for each case an in house monograph.

Quality control of drug product
The product specifications cover appropriate parameters for this dosages form. Validations of the analytical methods have been presented.

Batch analysis has been performed on several batches. The batch analysis results show that the finished products meet the specifications proposed.

The compliance of the packaging materials with the Ph. Eur. requirements is guaranteed.
In accordance with the Directive of 2001/83/EC and the Guideline (CPMP/QWP/4359/03) on Plastic Immediate Packaging is the suitability of the container closure system discussed. This was discussed consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage from (including sorption to container and leaching), safety of materials of construction and performance(such as reproducibility of the dose delivery from the device when presented as part of the drug product). Cholecalciferol is stated to be sensitive to heat, oxygen and UV-light. The storage statement should be restricted to: “Store in the original package, in order to protect from light”.

Stability of drug product
Stress testing study on API, excipients and finished product was performed and report is

presented in the documentation. The only degradation products detected during stability is trans-cholecalciferol. That is not toxic and it is not possible to set a specification limit for the control of the finished product. The supportive data are sufficiently discussed.
Degradation products have been monitored during stability testing. Their monitoring is especially important because of the high variability of the assay method, which hampers and appropriate assessment of the cholecalciferol degradation.
The photosensitivity of the drug product is investigated in accordance with "Note for Guidance on the Photostability testing of New Active Substances and Medical products. The results are included in the Stress testing report presented in the documentation.

The proposed shelf-life of **24 months** with the special precautions for storage "Do not store above 30°C. Store in the original carton to protect the cartons from light".

II.4 Discussion on chemical, pharmaceutical and biological aspects

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.

III. NON-CLINICAL ASPECTS

No own non-clinical studies have been performed. Instead the preclinical expert refers to data available in public domain. Cholecalciferol is widely used in the medical practice in Europe. The pharmacology, pharmacokinetic and toxicology is well known and exhibit an established safety profile. Non-clinical aspects are addressed in SmPC and PIL sufficiently.

III.1 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 a sufficient justification for not submitting an ERA can been provided by the authorisation holder. Nevertheless the marketing authorisation holder has provided a short and sufficient estimation of the potential environmental exposure which ensured that an environmental risk is not expected by the active substance.

III.2 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 to ensure safety use of the product.

IV. CLINICAL ASPECTS

IV.1 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 and 100.00 IU, drink from Laboratoires S.M.B. S.A.

The product is indicated for starting treatment of Vitamin D deficiency in adults.

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

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

IV.2 Pharmacokinetics

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

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.

IV.4 Clinical efficacy

The medicinal product is indicated for starting treatment of vitamin D deficiency.
The dosage must be determined individually by the treating doctor.
For starting treatment of vitamin D deficiency and under medical supervision a cumulative dose of 100.000 IU over 1 week is recommended. 1 Ampoule of D-CURA 100.000 IU may be given as a single dose or 4 ampoules of D-CURA 25.000 IU weekly may be given.

Additional necessary treatment with D-CURA must be decided by the treating doctor. Serum levels of 25-hydroxycalciferol and calcium should be monitored after initiation of treatment. The necessity of further monitoring can be individualised, guided by the dose administered and by the individual patient's needs. Starting treatment of vitamin D deficiency should be followed by a maintenance therapy dose of cholecalciferol. Maintenance therapy requires lower strength formulations.

The use in the paediatric population is contraindicated. Further contraindications are hypersensitivity to the active substance or to any of the excipients, hypercalcaemia and/or hypercalciuria, neprhrolithiasis, serious renal impairment, hypervitaminosis D, and Pseudohypoparathyroidism.

D-CURA should only be taken during pregnancy if clearly needed and only at doses that are absolutely necessary to eliminate the deficiency.
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.

IV.5 Clinical safety

The overall assessment of safety is based on a substantial time period of well-established use of cholecaciferol.
Side effects of treatment with Vitamin D result from overdose. Overdose can lead to hypercalcaemia with acute symptoms such as cardiac arrhythmias, nausea, vomiting, psychic symptoms, disturbances of consciousness. As chronic symptoms increased urgency to urinate, increased thirst, loss of appetite and weight, kidney stones, kidney calcification, calcification in tissues outside the skeleton can occur. A fatal outcome has been reported.
In order to avoid overdosing patients at risk have to be excluded from administration. 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

The applicant has provided documents that set out a detailed description of the Laboratoires S.M.B. system of pharmacovigilance (Version 9.0 dated April 2012). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

IV.7 Discussion on the clinical aspects

Based on the clinical data available at the time of authorization D-CURA 25.000 IU and D-CURA 100.00 IU were assessed as sufficiently effective and safe for starting treatment of Vitamin D deficiency.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit-risk-ratio is considered positive at the time of authorization.

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
DE/H/2903/002 /IB/001	Change in the (invented) name of the medicinal product for Nationally Authorised Products	No	17-7-2013	Approved	N.A.
DE/H/2903/001 -2/IB/002	Change in the shelf-life or storage conditions of the finished product Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	Yes	8-7-2013	Approved	N.A.
DE/H/2903/001 -2/IA/003	Change in pack size of the finished product Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Yes	28-6-2013	Approved	N.A.
DE/H/2903/001 -2/IA/004/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - New certificate from a new	No	24-1-2014	Refused	Not available

	manufacturer (replacement or addition)				
DE/H/2903/001-2/IA/005/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - New certificate from a new manufacturer (replacement or addition)	No	7-5-2014	Approved	N.A.
DE/H/2903/001-2/IB/006/G	Change in the (invented) name of the medicinal product for Nationally Authorised Products	No	5-2-2015	Approved	N.A.
DE/H/2903/001-2/IA/007	Change in the batch size (including batch size ranges) of the finished product Up to 10-fold compared to the originally approved batch size	No	22-12-2014	Approved	N.A.
DE/H/2903/001-2/IA/008	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	No	19-5-2015	Approved	N.A.
DE/H/2903/001-2/IA/009	Introduction of, or changes to, a summary of	No	12-8-2015	Approved	N.A.

	pharmacovigilance system for medicinal products for human use Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location				
DE/H/2903/001-2/IB/010	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products Other variation	Yes	14-4-2016	Approved	N.A.
DE/H/2903/001/2/R/001	Renewal	No	28-9-2018	Approved	N.A.
DE/H/2903/001-2/IA/012	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product Secondary packaging site	No	2-5-2017	Approved	N.A.
DE/H/2903/001-2/IB/011/G	Change in pack size of the finished product Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Yes	11-5-2017	Refused	Not available
DE/H/2903/001-2/IB/013	Change in container closure system of the Finished Product Other variation	Yes	6-9-2017	Approved	N.A.
DE/H/2903/001-2/IB/014/G	Change in the (invented) name of the medicinal product for Nationally Authorised Products Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use Introduction of a summary of pharmacovigilance system, changes in	Yes No	11-11-2020	Approved	N.A.

	QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location				
DE/H/2903/001/IB/015	Change in pack size of the finished product Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Yes	23-8-2021	Approved	N.A.
DE/H/2903/001/IA/016	Change in pack size of the finished product Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Yes	2-12-2021	Refused	Not available
DE/H/2903/001-2/IA/017	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. -Updated certificate from an already approved manufacturer	No	1-3-2023	Approved	N.A.
DE/H/2903/001-2/II/018	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality,	Yes	23-5-2024	Approved	N.A.

	preclinical, clinical or pharmacovigilance data.				