COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dexmono 1 mg/ml eye drops, solution (dexamethasone sodium phosphate)

NL License RVG: 125622

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Dexmono. The marketing authorisation was granted on 20 July 2021. 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
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Dexmono 1 mg/ml eye drops, solution, from Rockmed Pharma B.V.

The product is indicated for the treatment of non-infectious inflammatory conditions affecting the anterior segment of the eye.

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

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Monofree Dexamethason by Laboratoires Théa (RVG 18658) which has been registered in Netherlands since 1997 (original product). The current application is packaged in a multidose container instead of a single dose preparation.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dexmono is a clear, colourless, water-like solution with a pH between 7.1 and 8.1. The osmolarity of the solution is between 250 and 290 mOsmol / kg.

The product contains 1.093 mg of dexamethasone sodium phosphate per ml of solution equivalent to 1 mg dexamethasone phosphate.

The solution is packed in a white LDPE bottle with a drop dispenser for multiple dosages (HDPE and silicone) with a sealed HDPE screw-cap.

The excipients are disodium phosphate dodecahydrate (E339), sodium chloride, disodium edetate, hydrochloric acid (E507) and/or sodium hydroxide (E524) for pH adjustments and water for injections.

II.2 Drug Substance

The active substance is dexamethasone sodium phosphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a hygroscopic white or almost white powder, is freely soluble in water and slightly soluble in ethanol. The drug substance does exhibit polymorphism. However, this is not relevant for the drug product as the drug substance is completely dissolved.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. No description of the applied analytical methods, their validation and justification of specifications is included, reference is made to the Ph. Eur. monograph, Ph. Eur. general texts and the CEP. This is acceptable. Furthermore, a test for microbiological purity has been added to the specification. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance has been provided for three production-scaled batches stored at 40ºC / 75% RH up to 6 months, at 25ºC / 60% RH up to 24 months and at 2-8 ºC up to 24 months in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. No photostability study has been performed. As the Ph. Eur. monograph for Dexamethasone Sodium phosphate requires storage protected from light, additional photostability studies are not considered necessary. Based on the data submitted, a retest period could be granted of 24 months with the following storage conditions: store in refrigerator (5ºC±3ºC). Keep the bags tightly closed to protect from moisture and store in the original packaging to protect from light.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified and their functions explained. The development of the product is based on the qualitative composition and physico-chemical properties of the reference product. Essential similarity of drug product at issue with the reference product from a physico-chemical point of view has been adequately demonstrated. The formulation contains no preservatives and is presented in a multi-dose container whose properties ensure maintenance of sterility throughout in-use shelf life. The selection of sterilisation method is adequately justified based on the incompatibility of the selected container with other sterilisation processes. The choice of kind

of filters and their compatibility with drug product are discussed, together with the development of the filtration process.
Extensive information is provided about the container system, including discussion about the functioning principles, drawings and presentation of the functional and microbiological studies performed on it by both the supplier and the drug product manufacturer. The MAH provided results of density and surface tension of the products used in the functionality studies of the packaging system and of the drug product subject of this application. The results of these additional parameters are identical regarding density and very similar regarding surface tension. The physicochemical similarity of the drug product with the reference product subject of this application is considered confirmed and therefore it is acceptable to extrapolate the results of functionality studies of the packaging system performed with the first to the latter. Closure integrity, usability, extractables and leachables studies have been performed. The container components are sterilized, all above mentioned tests are performed on irradiated samples. Further, a compound is included in the container tip to avoid bacterial growth on residual drop. Demonstration that the quantity of this compound present is adequate for the purpose and safe is provided, by studies performed on drug product subject of this application.

Manufacturing process

The manufacturing process includes the following steps: sterilisation of container components, compounding of bulk solution, filtration of solution, filling and sealing of bottles. The manufacturing process description contains a sufficient level of details. Holding time (max 24 hours) is defined between compounding and end of filtration. In-process controls are described in detail, bioburden is tested before and after the pre-filter. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches. The process validation report for the sterilisation process of the containers is provided and is adequate in line with the relevant guidelines. Filter validation studies have been adequately performed, including filter capacity, compatibility with drug product, extractables and establishment of filter integrity test parameters.

Control of excipients

The excipients comply with Ph. Eur. requirements and are tested for microbiological quality by the Drug product manufacturer. These specifications are acceptable.

Microbiological attributes

Microbiological challenge studies confirm that the containers are capable of maintaining sterility of the content and integrity during the proposed in-use period, under normal and worst case conditions. The MAH performed a worst-case in-use challenge study with drug product subject of this application. The full report is provided, together with the validation reports of the microbial count methods used for evaluation of results. The study protocol is described in detail and is considered an adequate challenge study, taking into account the maximal use and dosage of drug product at issue. All results were negative (no growth), confirming the suitability of the proposed container to maintain sterility of the content even in an extreme challenge situation. The pharmaceutical development of the product has been adequately performed.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, extractable volume, pH, osmolality, identification, assay of dexamethasone phosphate, related substances, sterility and the tightness of bottles. A test for water loss is performed only in stability studies. A sufficiently detailed description of all analytical methods is provided. An adequate discussion on organic impurities is provided. A risk assessment in line with ICH Q3D requirements is provided as justification for not testing for elemental impurities at release and is agreed. A discussion about residual solvents in line with ICH Q3C is provided. A risk assessment on possible contamination with nitrosamines is provided, the risk is considered to be low. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full-size batches from the proposed production site have been provided, demonstrating compliance with the specification.

Container closure system

Information about suppliers, materials, functioning, specifications and drawings of the container components is provided, together with certificates of analysis. The MAH has stated which type of material is used for drug product at issue, this is acceptable. Certificates of analysis representative of the chosen type of components and in line with the proposed specifications are provided.

Stability of drug product

Stability data on the product have been provided for three commercial-scaled batches stored under long term (25±2°C, 60±5% RH, up to 36 months), intermediate (30±2°C, 65±5% RH, up to 36 months) and accelerated (40±2°C, 75±5% RH, up to six months) conditions in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life was granted of 36 months with no special storage conditions required. Reports on forced degradation, freeze-thaw and photostability studies are provided. Drug product is stable when exposed to freeze-thaw cycles or light. In-use stability studies are performed on samples of about 6 months and 36 months (end of shelf life). The in-use stability studies are adequately set up. Based on these results, together with functional and microbiological studies on the container during use period, the proposed in-use shelf life of 28 days is agreed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Dexmono has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

- The in-use stability study of the drug product will be repeated towards the end of shelf-life

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dexmono is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Monofree Dexamethason which is available on the Dutch market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamethasone sodium phosphate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this hybrid application, the MAH has submitted no bioequivalence studies, which is considered acceptable.

IV.2 Pharmacokinetics

Biowaiver
A waiver of in vivo studies, based on physicochemical similarity to the reference product, has been requested. An essential similarity study has been performed, comparing physicochemical characteristics of three batches of the proposed product and three batches of the reference product. All results were in line with each other. The (amounts of) excipients of this aqueous solution are similar to the reference product. Furthermore, the results of the density and clarity comparability tests are identical in test and reference product. The essential similarity of test and reference product is confirmed. A waiver of the need to provide therapeutic equivalence data is considered acceptable.

IV.3 Risk Management Plan

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 Dexmono.

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

Important identified risks	- None
Important potential risks	- None
Missing information	- None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Monofree Dexamethason. No new clinical studies were conducted. The MAH demonstrated through a physicochemical similarity study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 test consisted of a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The language used for the purpose of user testing the PIL 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

Dexmono 1 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Monofree Dexamethason. Monofree Dexamethason is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

However, an opinion procedure was started regarding the functionality of the packaging system, the microbial challenge studies of the containers and the risk evaluation of nitrosamines. These were addressed adequately by the MAH and no other issues remained.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dexmono with the reference product, and have therefore granted a marketing authorisation. Dexmono was authorised in the Netherlands on 22 July 2021.

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