COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dexamethasone Medochemie 4 mg/ml, solution for injection/infusion (dexamethasone sodium phosphate)

NL/H/5436/001/DC

Date: 27 February 2024

This module reflects the scientific discussion for the approval of Dexamethasone Medochemie 4 mg/ml. The procedure was finalised on 9 February 2023. 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
HPLC	High-Performance Liquid Chromatography
HPLC-PDA	High-Performance Liquid Chromatography-Photodiode Array
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 Dexamethasone Medochemie 4 mg/ml, solution for injection/infusion, from Medochemie Ltd.

The product is indicated for:
Systemic use

- Cerebral oedema associated with cerebral tumour, neurosurgical procedures, cerebral abscess, bacterial meningitis
- Polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
- Severe, acute asthma attack
- Initial parenteral treatment of extensive, acute, severe skin diseases like erythroderma, pemphigus vulgaris, acute eczema
- Initial parenteral treatment of autoimmune diseases like systemic lupus erythematosus (especially visceral forms)
- Active rheumatoid arthritis with a severe, progressive course, e.g. fast proceeding destructive forms and/or with extra-articular manifestations
- Severe infectious diseases with toxic conditions (e.g. tuberculosis, typhoid, brucellosis) only with simultaneous anti-infectious therapy
- Palliative therapy of malignant tumours
- Prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti-emetic regimens
- Treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12+ with body weight >40 kg) who require supplemental oxygen therapy.

Local application

- Intraarticular injection: persistent inflammation of one or few joints after general management of chronic inflammatory joint diseases, activated osteoarthritis, acute forms of periarthropathia humeroscapularis
- Infiltration therapy: non-bacterial tenosynovitis and bursitis, peri-arthropathy, insertional tendinopathy
- Ophthalmology: subconjunctival administration in non-infectious keratoconjunctivitis, scleritis (except necrotising scleritis), uveitis anterior and intermedia.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and European Reference Product (ERP) Fortecortin Inject 4 mg Injektionslösung in einer Ampulle,

which has been registered by Merck Serono GmbH in Germany (national authorisation number: 9739.00.00) on 18 January 1996.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Croatia, Estonia, Latvia, Lithuania, Malta, Portugal, Romania, Slovenia and Spain.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. The assessment concluded that Dexamethasone, bedaquiline, delamanid, pretomanid, and para-aminosalicylic acid are different active substances that do not have the same principal molecular structural features and they have distinct mechanism of actions and thus the products are not considered to be similar. It is therefore concluded that there are currently no other products similar to dexamethasone approved for the orphan indication 'Treatment of tuberculosis'.

II. QUALITY ASPECTS

II.1 Introduction

Dexamethasone Medochemie is a solution for injection or infusion. It is a clear, colourless to slightly yellowish solution, with a pH of 7.0 to 8.5. It has an osmolality of 160 to 230 mOsm/kg.

The solution contains 4 mg/ml of active substance dexamethasone phosphate (as dexamethasone sodium phosphate).

The excipients are: sodium citrate (E331), disodium edetate (E386), creatinine, water for injections, sodium hydroxide (E524) (for pH adjustment) and concentrated hydrochloric acid (E507) (for pH adjustment).

The solution is packed in type I clear glass ampoules with 2 ml capacity, filled with 1 mL or 2 mL solution. The ampoules are packed in boxes.

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 powder and is freely soluble in water. Although polymorphism is known for dexamethasone sodium phosphate, it is not relevant for the current drug product as it concerns a solution.

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 Ph.Eur.

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. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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. Information has been provided which sufficiently supported the use of the product in the paediatric population. The development of the product has been described, the choice of excipients is justified and their functions explained. Because literature on the composition of the reference product was limited, several batches of the reference product were analysed to quantify the excipients and create a full profile for comparison to the new product. Different studies were executed to determine the pH of the formulation, the amount of excipients, the order of administration of the active substance and excipients and the scale-up of the production. The batches were placed under ICH stability conditions. The pharmaceutical development of the product has been adequately performed. The choices of the packaging and manufacturing process have been justified, as well as the selection of the sterilisation process.

Manufacturing process
The manufacturing process consists of mixing, pH adjustment, filtration and packaging. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph. Eur. and USP requirements. These specifications are acceptable.

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 description, pH, clarity and colour of solution,

extractable volume, identification (HPLC and HPLC-PDA), related substances, assay of creatinine, assay of dexamethasone phosphate, particulate contamination (visible particles and sub-visible particles), sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation on the presence of nitrosamine impurities in the drug product has been provided, showing there was no risk for this product. The release and shelf-life requirements are identical, except for the limits of assay of creatinine and related substances. In particular, wider limits were acceptable for some impurities at shelf life.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three production-scaled batches have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches for the 4 mg/1 ml volume and three production scaled batches for the 8 mg/2 ml volume, stored at 25°C/ 60% RH (18 months for 4 mg/1 ml and 24 months for 8 mg/2 ml) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline, except for the intermediate condition where a higher relative humidity of 75% was used, which was acceptable. On basis of the data submitted, a shelf life was granted of 18 months (for 4mg/1ml) and 24 months (8mg/2ml), which are acceptable on the basis of the provided long term stability data. The labelled storage conditions are must be stored at a temperature below 25°C, and keep the ampoules in the outer carton, in order to protect from light.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light.

In-use stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 hours following dilution with isotonic saline solution, Ringer's solution, glucose solution 5%, glucose solution 10% or dextrose solution 5%, when stored at 25°C or 2–8°C.

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

There are no substances of animal origin present in the product (creatinine is of synthetic origin), 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 member states consider that Dexamethasone Medochemie has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Dexamethasone has endocrine disrupting properties. Therefore, the MAH was asked to provide a full Phase II ERA or a justification for the lack of its absence, taking into account that dexamethasone is an endocrine active substance. It was concluded that dexamethasone is considered not persistent, bioaccumulative and toxic (PBT) or very persistent (vPvB). The conclusion on the risks of dexamethasone to the environment cannot be drawn in absence of reliable studies.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Fortecortin Inject which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. However, the applicant has provided a commitment to perform additional tests in order to form a conclusion on the risks of the active substance to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamethasone sodium phosphate is a well-known active substance with an established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required (see section IV.2).

IV.2 Pharmacokinetics

Dexamethasone Medochemie 4 mg/ml, solution for injection/infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on

bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Dexamethasone Medochemie is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy and safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (RMP), 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 Dexamethasone Medochemie.

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

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients >70 years old and in particular >80 years old (COVID-19 indication) Safety in pregnant women (COVID-19 indication)

The member states 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 Fortecortin. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Dexamethasone Medochemie 4 mg/ml solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Fortecortin Inject 4 mg Injektionslösung in einer Ampulle. Fortecortin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dexamethasone Medochemie with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 February 2023.

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
-	-	-	-	-	-