COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dexamethasonfosfaat Accord 4 mg/ml solution for injection/infusion (dexamethasone sodium phosphate)

NL/H/5564/001/DC

Date: 2 March 2026

This module reflects the scientific discussion for the approval of Dexamethasonfosfaat Accord 4 mg/ml solution for injection/infusion. The procedure was finalised on 15 May 2024. 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 Dexamethasonfosfaat Accord 4 mg/ml solution for injection/infusion, from Accord Healthcare B.V.

The product is indicated for:

Systemic use

Intravenous or intramuscular administration

Dexamethasonfosfaat Accord is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions:

- Cerebral oedema caused by cerebral tumour, neurosurgical interventions, cerebral abscess, bacterial meningitis
- Posttraumatic shock and prevention of posttraumatic acute respiratory distress syndrome (ARDS)
- Coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy
- Anaphylactic shock (following initial epinephrine injection)
- Severe acute asthma attack
- Initial parenteral treatment of extensive, acute, severe skin diseases, such as erythroderma, pemphigus vulgaris, acute eczema
- Initial parenteral treatment of autoimmune diseases, such as systemic lupus erythematosus (in particular visceral forms)
- Active rheumatoid arthritis with a severe progressive course, e.g. rapidly destructive forms and/or with extraarticular manifestations
- Severe infectious diseases with toxic states (e.g. tuberculosis, typhus, brucellosis) only with appropriate anti-infective therapy
- Palliative therapy for malignant tumours
- Prophylaxis and therapy of postoperative or cytostatic-induced vomiting in the context of antiemetic regimens

Subcutaneous administration

- Palliative therapy for malignant tumours and prevention and treatment of chemotherapy-induced nausea and vomiting (CINV)

In palliative care, patients receiving corticosteroids for symptoms such as fatigue, anorexia, refractory nausea and vomiting or adjuvant analgesia and symptomatic treatment of cord compression or raised intracranial pressure, Dexamethasonfosfaat Accord may be administered subcutaneously as an alternative to the oral route when the latter is unacceptable or no longer feasible.

Local administration

- Intraarticular and periarticular injections for persistent inflammation in one or several joints after general treatment of chronic inflammatory joint disease, activated arthrosis, acute forms of periarthropathia humeroscapularis
- Infilteration therapy (when strictly indicated) for non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy

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 a 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) since 18 January 1996.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Finland, Germany, Hungary, Iceland, Ireland, Norway, Poland, Portugal, Slovenia, Spain and Sweden.

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. A similarity assessment has been performed between Dexamethasonfosfaat Accord and the currently approved orphan medicinal products for the treatment of tuberculosis:
Granupas (EU Orphan Designation Number EU/3/10/826, granted on 17 December 2010)
Deltyba (EU Orphan Designation Number EU/3/07/524, granted on 1 February 2008)
Dovprela (EU Orphan Designation Number EU/3/07/513, granted on 29 November 2007)
Sirturo (EU Orphan Designation Number EU/3/05/314, granted on 26 August 2005)

The similarity assessment report was completed in May 2023, concluding the products were not similar based on mechanism of action and principal molecular structure. This was reflected in the indications and the procedure was therefore acceptable.

II. QUALITY ASPECTS

II.1 Introduction

Dexamethasonfosfaat Accord is a clear colourless solution for injection/infusion with pH 7.00 – 8.50.

Each 1 ml of solution for injection/infusion contains 4.0 mg of dexamethasone phosphate (as dexamethasone sodium phosphate).

Each 2 ml of solution for injection/infusion contains 8.0 mg of dexamethasone phosphate (as dexamethasone sodium phosphate).

Each 5 ml of solution for injection/infusion contains 20.0 mg of dexamethasone phosphate (as dexamethasone sodium phosphate).

The excipients are: creatinine, disodium edetate (E385), sodium citrate (E331), sodium hydroxide (to adjust the pH) (E524) and water for injection.

The solution for injection/infusion is packed in the following materials:
1 ml: 2 ml type I clear glass vial with chlorobutyl rubber stopper and aluminum flip off blue seal.
2 mL: 2 ml type I clear glass vial with chlorobutyl rubber stopper and aluminum flip off plain light blue seal.
5 ml: 6 ml type I clear glass vial with chlorobutyl rubber stopper and aluminum flip off plain light blue seal.

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 very 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. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 24 months 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. The choice of excipients is justified and their functions explained. The composition of the product is substantiated. Analysis of the composition of the reference product was performed. Different studies were executed for the formulation and process development. Batches were placed on stability studies, confirming an acceptable composition and scale-up of the production process. 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 which is in line with the Ph.Eur. requirements.

Manufacturing process

The manufacturing 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., British Pharmacopoeia (BP) and in-house requirements. These specifications are acceptable.

Microbiological attributes

The container closure integrity is demonstrated: all three batches of each packaging (the 1 ml size in a 2 ml vial, the 2 ml size in the 2 ml vial and the 5 ml size in a 6 ml vial) complies with the test. The integrity of the packaging is sufficiently demonstrated.

The leachable study is performed to monitor unknown peaks observed above Analytical Evaluation Threshold (AET) levels in the extractable study.
The leachable study report shows that, no any potential leachable were observed in drug product. Hence it is concluded that the leachable study data complies with the Product Quality Research Institute (PQRI) guidance and the selected container closure is suitable for proposed product.

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, identification, alkalinity (pH), extractable volume, clarity and colour of solution, assay, related substances, particulate contamination (sub visible), bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. The information as provided is sufficient to conclude the risk of nitrosamine impurity formation is small.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches from the proposed production site 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 stored at 25°C/60% RH (24 months), 30°/75% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are "Store below 30°C. Keep the vial in the outer carton in order to protect from light.".

As indicated in the SmPC, the product can be added, without loss of potency, to sodium chloride 0.9%, glucose 5% or Ringer's solution and given by intravenous infusion. The results of the dilution study confirm the dilution (concentration 0.008 and 0.8 mg/ml) and stability of the drug product up to 48 hours in the dilution solutions 0.9% sodium chloride solution, 5% glucose solution and Ringer's solution when stored at 15°C-30°C. In-use stability data have been provided demonstrating that the product remains stable for 48 hours following dilution, when stored at 15-30°C.

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 member states consider that Dexamethasonfosfaat Accord 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)

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

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. Therefore, the member states 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Dexamethasonfosfaat Accord 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 Dexamethasonfosfaat Accord is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/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, 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 Dexamethasonfosfaat Accord. At the time of approval, the most recent version of the RMP was version 1.1 dated 3 May 2024.

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 Inject. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Dexamethasone phosphate Hameln 4 mg/ml solution for injection, SK/H/0220/001 (for text wording). The MAH declared that the PL design and layout is similar to that of Paclitaxel AHCL 6 mg/ml, concentrate for solution for infusion, NL/H/1444/001. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dexamethasonfosfaat Accord 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 Inject 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.

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 Dexamethasonfosfaat Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 May 2024.

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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.