CMDh/223/2005
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Public Assessment Report

Scientific discussion

Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion (hydrocortisone hydrogen succinate)

ES/H/0933/001/DC

Date: 16/03/2026

This module reflects the scientific discussion for the approval of Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion. The procedure was finalised at 11 June 2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion, from Laboratorios NORMON S.A.

The product is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. Endocrine disorders
Primary or secondary adrenocortical insufficiency.

2. Collagen diseases
Systemic lupus erythematosus.

3. Dermatological diseases
Severe erythema multiforme (Stevens-Johnson syndrome).y

4. Allergic states
Bronchial asthma, anaphylactic reactions.

5. Gastro-intestinal disease
Ulcerative colitis, Crohn's disease

6. Respiratory disease
Aspiration of gastric contents

7. Medical emergencies
Hydrocortisone is indicated in the treatment of shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenocortical insufficiency may be present.

8. Treatment of Acute Organ Transplant Rejection

9. Other medical conditions as hypothyroid coma, necrotizing vasculitis and rheumatoid arthritis

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

-*Type of marketing authorisation (legal basis). The following sentence can be used:*
"The marketing authorisation has been granted pursuant to Article of Directive 2001/83/EC."

Please specify in case the marketing authorisation is granted under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC

- *Main features of disease/condition etc.*

- *Whether a discussion in CMDh took place with reference to section V.*

- *Reference to the conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC in section V*

II. QUALITY ASPECTS

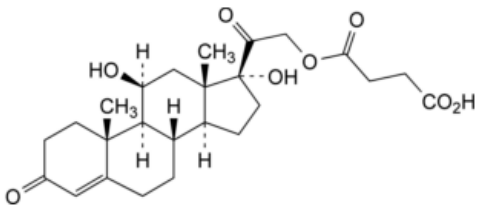
II.1 Introduction

The finished product is presented as a powder and solvent for solution for injection/infusion:
- The powder contains 133.7 mg of hydrocortisone sodium succinate equivalent to 100 mg of hydrocortisone. The powder is contained in type I glass vial of 2 mL.
- The solvent for reconstitution of the powder contains 2 mL of water for injection in type I colourless glass ampoule.

II.2 Drug Substance

The CEP procedure is used to support the quality of the drug substance hydrocortisone hydrogen succinate.

General information
Nomenclature:
INN: Hydrocortisone
Chemical name: 11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl hydrogen butanedioate.
CAS-No: [2203-97-6]
Structure:



Molecular formula: $C_{25}H_{34}O_8$
Molecular mass: 462.5
General Properties:
Hydrocortisone hydrogen succinate is white or almost white, hygroscopic power. Practically insoluble in water. It dissolves in dilute solutions of alkali carbonates and alkali hydroxides.

Manufacture, process controls and characterisation
As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis
Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system
As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability
Re-test period is included in the CEP. Stability studies of the active substance have been assessed by EDQM.

II.3 Medicinal Product

Description of the product
The finished product is presented as a powder and solvent for solution for injection/infusion in vials with white or almost white sterile lyophilized powder and ampoules with 2 mL of water for injection.
Other ingredients of the powder are disodium phosphate, monobasic sodium phosphate and sodium hydroxide.

Powder (vials):

Pharmaceutical Development
The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The proposed method of sterilization has been appropriately justified.

Manufacture of the product
The manufacturing process is fully described, and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients
Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis
The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted, and the results show that the finished product meets the proposed release specification.

Container closure system
The powder for solution for injection/infusion is packaged in type I glass vial of 2 mL.
The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability
Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Solvent (ampoules):

Pharmaceutical Development
The development of the product has been described, the only excipient of the solvent of the medicinal product is water for injection.
The proposed method of sterilization has been appropriately justified.

Manufacture of the product
The manufacturing process is fully described, and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients
The only excipient of the solvent of the medicinal product is water for injection, which complies with the specifications of the current Ph. Eur.

Product specification, analytical procedures, batch analysis
The specifications for the solvent (water for injection) of the medicinal product are adequate. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the solvent (water for injection) of the medicinal product meets the proposed release specification.

Container closure system
The solvent (water for injection) is packaged in type I colourless glass ampoule.
The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability
Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life:	2 years
Storage conditions:	Store below 30ºC. Keep the vial in the original package in order to protect from light.
In-use shelf-life:	After dilution, chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, the product should be used immediately.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone hydrogen succinate are well known. As hydrocortisone hydrogen succinate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Hydrocortisone 100 mg powder and solvent for solution for injection or infusion is a generic product, it will not lead to an increased exposure to the environment and therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Applicant has not conducted new clinical studies with this product. The efficacy of hydrocortisone is well known and has been documented over the years in numerous clinical studies.

For this generic application of an immediate release formulation, the MAH has not submitted any bioequivalence studies according to the *Guideline on the investigation of bioequivalence* since the proposed product is an aqueous solution intended for intravenous administration by injection or infusion containing the same active substance as the currently approved product.

IV.2 Pharmacokinetics

Pharmacotherapeutic group: Glucocorticoids, ATC Code: H02AB09

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

Biowaiver

According to the *Guideline on the investigation of bioequivalence*, if the test product is an aqueous intravenous solution at time of administration and contains an active substance (hydrocortisone hydrogen succinate) in the same concentration as an approved intravenous solution, bioequivalence studies may be waived.

The current application consists in a medicinal product in the same pharmaceutical form (powder and solvent for solution for injection or infusion) as the reference medicinal product Solu-Cortef 100 mg (powder and solvent for solution for injection or infusion). The applied product also contains qualitatively the same excipients in similar amounts as the reference product and the quantitative differences are not expected to affect the bioavailability.

The bioequivalence between the test and the reference product can be assumed.

IV.3 Pharmacodynamics

Pharmacology of the corticosteroids is complex and the drugs affect almost all body systems. Maximum pharmacologic activity lags behind peak blood concentrations, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drugs.
Aldosterone is a naturally occurring mineralocorticoid, and it affects electrolyte and fluid balance by acting on the distal renal tubule to promote sodium reabsorption and potassium and hydrogen excretion.
Although glomerular filtration rate is also increased which promotes sodium excretion, the net effect is almost always sodium retention with resultant edema and hypertension. The naturally occurring glucocorticoids, hydrocortisone (cortisol) and cortisone, have some mineralocorticoid activity in addition to their glucocorticoid activity. Synthetic glucocorticoids also exhibit some degree of mineralocorticoid activity, especially with prolonged, high-dose therapy.

IV.4 Clinical efficacy and safety

The efficacy and safety of medicinal products containing hydrocortisone have been well documented in numerous clinical trials and widespread clinical use, for the treatment of patients with a variety of diseases.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan (version 0.3, 21 April 2025), 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 Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion (hydrocortisone hydrogen succinate).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion.

IV.6 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the Guidance for the Pharmaceutical Industry on the use of BRIDGING STUDIES to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC.

The Daughter PIL and the Parent PIL were compared based on the following aspects:
• Visual Presentation: dimension, font size and style, pictures, bullet pointing, bolding, spacing and any colouring in the PILs.
• Textual: key safety messages, jargon, wording simplicity, and overall linguistic theme.

In conclusion, the design and layout of the parent leaflet and the daughter leaflet are common.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of for Hydrocortisone Normon 100 mg powder and solvent for solution for injection/infusion is considered adequate, there are no objections to the approval of this medicinal product from a non-clinical and clinical point of view.

The efficacy and safety of the active substance for Hydrocortisone, have been sufficiently demonstrated.

The product information is acceptable. The benefit/risk ratio is considered positive and therefore authorisation is recommended.