IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dexamethasone phosphate Noridem 4 mg/mL Solution for injection
Dexamethasone sodium phosphate
PA1122/020/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Dexamethasone phosphate Noridem 4 mg/mL Solution for Injection from Noridem Enterprises Limited on 28th May 2021 for the treatment of "certain endocrine and non-endocrine disorders responsive to corticosteroid therapy".

This decentralised application was submitted as an Article 10 (1) of Directive 2001/83 as amended, citing Decadron 3.3mg/ml solution for injection (PA0035/016/003) by Merck Sharp & Dohme Limited as the reference product.

With Ireland as the Reference Member State in this Decentralised Procedure, Noridem Enterprises Limited. Applied for the Marketing Authorisations for Dexamethasone phosphate Noridem 4 mg/mL Solution for injection in CMS: Hungary, Cyprus, Czech Republic, Slovakia & Greece

The legal basis for the application is Article 10(1) of 2001/83/EC a generic application.

The product will be subject to medical prescription that may not be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Dexamethasone phosphate Noridem 4 mg/mL Solution for injection
Name(s) of the active substance(s) (INN)	Dexamethasone sodium phosphate
Pharmacotherapeutic classification (ATC code)	H02AB02 dexamethasone
Pharmaceutical form and strength(s)	4 mg/mL Solution for injection
Marketing Authorisation Number(s) in Ireland (PA)	PA1122/020/001
Marketing Authorisation Holder	Noridem Enterprises Limited
MRP/DCP No.	IE/H/833/001/DC
Reference Member State	IE
Concerned Member State	CY CZ EL HU SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dexamethasone phosphate Noridem 4 mg/mL Solution for injection.

II.2 Drug substance

The active substance is Dexamethasone Sodium Phosphate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

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

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for solution for injection, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of the drug product, Dexamethasone phosphate Noridem 4mg/ml Solution for Injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Decadron 3.3mg/ml solution for injection (PA0035/016/003) (Merck Sharp & Dohme Limited) on the European market since 1978. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well known. As dexamethasone is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Dexamethasone phosphate Noridem 4 mg/mL Solution for injection is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well known. As dexamethasone is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamethasone phosphate is a well known active substance with established efficacy and tolerability. Dexamethasone phosphate is a glucocorticoid. Glucocorticoids are used in both endocrine and non-endocrine disorders.
They are administered as replacement therapy in patients with primary or secondary adrenal insufficiency, and as adrenal suppression therapy in congenital adrenal hyperplasia and glucocorticoid resistance. They are also used in patients with Grave's opthalmopathy and for some diagnostic purposes such as in establishing Cushing's syndrome. Moreover, due to their immunosuppressive and anti-inflammatory properties they are used in a broad range of non-endocrine disorders affecting many different systems.

The content of the SmPC approved during the decentralised procedure is generally in accordance with that accepted for the reference product Decadron first authorised in the UK in July 1987 to Merck Sharp & Dohme Limited (PL 00025/5045R), with any additional changes now accepted in the SmPC having been justified by the MAH. In the RMS Ireland, Decadron 3.3mg/ml solution for injection (PA0035/016/003) (Merck, Sharp and Dohme Limited) was first authorised in April 1978. However, the proposed reference medicinal product was withdrawn in IE (RMS) in 2003 and in the UK (CMS) in 2005. The applicant has confirmed the withdrawal was not due to safety reasons.

An additional route of administration, subcutaneous route, not authorised for the reference medicinal product Decadron, is considered acceptable in the palliative care setting based on the submitted justification and this route has been approved for Dexamethasone phosphate Noridem 4 mg/mL Solution for injection.

For this generic application, a bioequivalence study was not performed. Justification was provided based on the EU Guideline on the Investigation of Bioequivalence Appendix II for parenteral solutions that a BE study is not required.

The Guideline states the following:

"Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity.

Biowaiver

From a clinical perspective, a biowaiver was considered acceptable. Robust justification was provided that the proposed product can be considered comparable to the discontinued reference product. The proposed formulation is relatively simple, consisting of commonly used excipients which are used in other authorised Dexamethasone parenteral products in the EU. Comparable viscosity of the proposed product versus a number of comparator products, one of which could be considered essentially similar to the discontinued reference product has also been demonstrated. As such, the applicant was deemed to have met the requirements of CPMP/EWP/QWP/1401/98 Rev. 1.

IV.2 Pharmacokinetics

A summary of the bipharmaceutics, clinical pharmacology, efficacy and safety based on evidence from literature is provided in the overview. No new studies were conducted.
The biological half-life of dexamethasone in plasma is about 190 minutes.
Binding of dexamethasone to plasma proteins is less than for most other corticosteroids and is estimated to be about 77%. Up to 65% of a dose is excreted in the urine in 24 hours, the rate of excretion being increased following concomitant administration of phenytoin.
The more potent halogenated corticosteroids such as dexamethasone, appear to cross the placental barrier with minimal inactivation.

IV.3 Pharmacodynamics

A summary of the bipharmaceutics, clinical pharmacology, efficacy and safety based on evidence from literature is provided in the overview. No new studies were conducted. Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active members of its class. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. They cause profound and varied metabolic effects and in addition, they modify the body's immune responses to diverse stimuli. Naturally-occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.
Dexamethasone has predominant glucocorticoid activity with little propensity to promote renal retention of sodium and water. Therefore it does not offer complete replacement therapy and must be supplemented with salt or desoxycorticosterone.

IV.4 Clinical Efficacy

A summary of the bipharmaceutics, clinical pharmacology, efficacy and safety based on evidence from literature is provided in the overview. No new studies were conducted. As this is a generic application 10(1) legal basis and is bioequivalent to the reference product this is acceptable.

IV.5 Clinical Safety

A summary of the bipharmaceutics, clinical pharmacology, efficacy and safety based on evidence from literature is provided in the overview. No new studies were conducted. As this is a generic application 10(1) legal basis and is bioequivalent to the reference product this is acceptable.
Risk Management Plan

The applicant 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 Dexamethasone Phosphate 4mg solution for injection.
The revised RMP (version 0.3, dated 9/09/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of safety concerns

Important identified risks	Growth retardation in children Neurodevelopmental adverse events in pre-term neonates.
Important potential risks	Tumour lysis syndrome Foetal developmental toxicity Use during lactation
Missing information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

This is an abridged Marketing Authorisation Application (MAA) submitted under the legal basis of Article 10(1) of Council Directive 2001/83/EC, as amended.

Dexamethasone phosphate 4 mg/mL Solution for injection, was considered essentially similar to the Reference Medicinal Product (RMP) Decadron 3.3mg/ml solution for injection (Merck, Sharp and Dohme Limited; PA0035/016/003, containing 3.3mg/ml of dexamethasone base; or 4mg/ml of dexamethasone phosphate), which was first authorised in RMS IE in 1978. The reference product has now been withdrawn from the Irish and UK markets. The applicant confirmed this was not due to any safety concern.

A bioequivalence study is not required as it meets the requirements set out in the EU Guideline on the Investigation of Bioequivalence Appendix II for parenteral solutions.
From a quality and clinical perspective, the biowaiver requested was considered acceptable.

V. OVERALL CONCLUSIONS

Dexamethasone phosphate Noridem 4mg/ml Solution for Injection is a generic form of Decadron 3.3 mg/ml solution for injection (Merck, Sharp and Dohme Limited; PA0035/016/003, containing 3.3mg/ml of dexamethasone base; or 4mg/ml of dexamethasone phosphate). Dexamethasone phosphate is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The legal basis for the application is Article 10(1) of 2001/83/EC a generic application.

The product will be subject to medical prescription that may not be renewed.

No bioequivalence studies were conducted and the biowaiver was considered acceptable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that a biowaiver ise accepted for Dexamethasone phosphate Noridem 4mg/ml Solution for Injection and that the product is comparable to the reference product. Comparable viscosity of the proposed product versus a number of comparator products, one of which could be considered essentially similar to the discontinued reference product has also been demonstrated. As such, the applicant is deemed to have met the requirements of CPMP/EWP/QWP/1401/98 Rev. 1. A satisfactory risk/benefit profile for Dexamethasone phosphate Noridem 4mg/ml Solution for Injection was thus demonstrated and therefore a marketing authorisation could be granted.

VI. REVISION DATE

02.11.2025