IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dexamethasone phosphate 4mg/ml Solution for Injection or Infusion
Dexamethasone sodium phosphate
PA0281/237/002

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5643/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20/06/2018 under procedure number IE/H/0609/1/DC
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/237/002
Marketing Authorisation Holder: Pinewood Laboratories Ltd

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Dexamethasone 3.3 mg/ml Solution for Injection or Infusion (PL 14682/0023; UK/H/5643/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated in adults and children for all forms of general and local glucocorticoid injection therapy and all acute conditions in which intravenous glucocorticoids may be life-saving.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Decadron Injection, 3.3 mg/ml, which was originally granted in the UK on 31 July 1987 to Merck Sharp & Dohme Limited (PL 00025/5045R). The reference medicinal product has now been withdrawn from the UK market for commercial reasons since 2005. The RMS considers the legal basis and cited reference medicinal product for this submission acceptable as no exclusivity period is applicable in this instance.

Dexamethasone is a potent synthetic member of the glucocorticoid class of steroid hormones. It acts as an anti-inflammatory and immunosuppressant. Its potency is about 40 times that of hydrocortisone (Goodman & Gilman), marketed in Europe for more than 30 years. Adrenocorticoids act on the hypothalamic-pituitary-adrenal system (HPA) at specific receptors on the plasma membrane. On other tissues the adrenocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors which enter the cell nucleus and stimulate protein synthesis. Adrenocorticoids have anti-allergic, antitoxic, antishock, antipyretic and immunosuppressive properties. Dexamethasone has only minor mineralocorticoid activities and does therefore, not induce water and sodium retention.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 199) on 12 December 2014. After a subsequent national phase, a licence was granted in the UK on 15 January 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

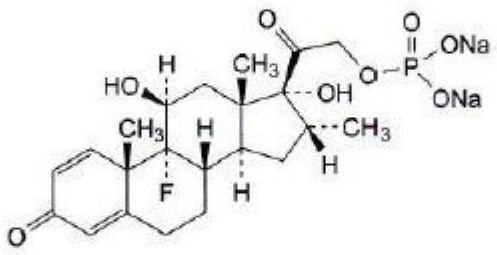
II.1 Introduction

Each ml of solution (for injection or infusion) contains 3.3 mg dexamethasone (as sodium phosphate) which is equivalent to 4 mg dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate. Each 2 ml of solution (for injection or infusion) contains 6.6 mg dexamethasone (as sodium phosphate) which is equivalent to 8 mg dexamethasone phosphate or 8.74 mg dexamethasone sodium phosphate. Other ingredients consist of the pharmaceutical excipients creatinine, ascorbic acid (E300), sodium citrate (E331), water for injections and sodium hydroxide (E524) [for pH adjustment]. The finished product is packed into 1ml and 2ml colourless, neutral, type I glass ampoules and is available in pack sizes of 5 ampoules (both 1ml and 2ml) or 10 ampoules (1ml size only). Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN:	Dexamethasone sodium phosphate
Chemical name:	9-fluoro-11ß,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate

Structural formula:



Molecular formula:	$C_{22}H_{28}FNa_2O_8P$
Molecular mass:	516.4
Appearance:	A white or almost white, very hygroscopic powder.
Solubility:	Freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride and ether.

Dexamethasone sodium phosphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, dexamethasone sodium phosphate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, solution for injection or infusion containing 3.3 mg dexamethasone (as sodium phosphate) per ml that was comparable in performance to the originator product Decadron Injection, 3.3 mg/ml (Merck Sharp & Dohme Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of creatinine which is controlled to the United States Pharmacopeia and National Formulary (USP-NF) standards. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 21 months for the unopened ampoule with the storage conditions 'Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.'
For storage conditions after dilution of the medicinal product, see section 6.3 of the SmPC.

Shelf-life after dilution of the medicinal product:
Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and in daylight conditions when diluted with the infusion fluids listed in 6.6 of the SmPC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for Dexamethasone 3.3 mg/ml Solution for Injection or Infusion. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Dexamethasone 3.3 mg/ml Solution for Injection or Infusion 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.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), "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."

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of dexamethasone.

Based on the data provided, Dexamethasone 3.3 mg/ml Solution for Injection or Infusion can be considered bioequivalent to Decadron Injection, 3.3 mg/ml (Merck Sharp & Dohme Limited, UK).

IV.2 Pharmacokinetics

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (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 3.3 mg/ml Solution for Injection or Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	Risk of susceptibility and infection worsening.
	Risk of severe adverse reactions in case of hypersensitivity to any ingredient.
	Risk of tumour lysis syndrome in patients with haematological malignancies.
	Risk of severe psychiatric adverse reactions.
	Risk of serious anaphylactoid reactions, such as glottis oedema, urticaria and bronchospasm, particularly in patients with a history of allergy.
	Risk of harmful effects if used for the management of head injury or stroke.
	Risk of increased in mortality if therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS).
	Risk of neurodevelopmental adverse events in premature infants.
	Risk of adrenal cortical atrophy during prolonged therapy.
	Risk of withdrawal symptoms in case of withdrawal of a prolonged therapy
	Risk of potential fatal infection in case of exposure to chickenpox.
	Risk of severe infection in case of exposure to measles.
	Risk of diminished antibody response to vaccines.
	Risk of worsening of such conditions: Osteoporosis, Hypertension or congestive heart failure, Existing or previous history of severe affective disorders, Diabetes mellitus (or a family history of diabetes), History of tuberculosis, Glaucoma (or a family history of glaucoma), Previous corticosteroid-

Summary of safety concerns	
	induced myopathy, Liver failure, Renal insufficiency, Epilepsy, Gastro-intestinal ulceration, Migraine, Certain parasitic infestations in particular amoebiasis, Incomplete statural growth, Patients with Cushing's syndrome.
	Risk of ruptured tendon.
	Risk of growth retardation in infancy, childhood and adolescence.
	Risk of more serious consequences in old age in case of common adverse effects of systemic corticosteroids.
	Risk of cardiovascular collapse after rapid intravenous injection of massive doses.
Important potential risks	Risk of development of cerebral palsy in preterm infants.
	Risk of abnormalities of foetal development e.g. cleft palate, intra-uterine growth retardation, brain growth and development
	Risk of hypoadrenalism in neonates
Important missing information	No data on fertility are available for dexamethasone
	There are no data on dexamethasone during lactation

ummary table of risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of susceptibility and infection worsening.	Specific statement in section 4.3 of SmPC	Patients in UK should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.
Risk of severe adverse reactions	Specific statement in section 4.3	NA

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
in case of hypersensitivity to any ingredient.	of SmPC	
Risk of tumour lysis syndrome in patients with haematological malignancies.	Specific statement in section 4.4 of SmPC	NA
Risk of severe psychiatric adverse reactions.	Specific statement in section 4.4, 4.5 and 4.8 of SmPC	NA
Risk of serious anaphylactoid reactions, such as glottis oedema, urticaria and bronchospasm, particularly in patients with a history of allergy.	Specific statement in section 4.4 of SmPC	NA
Risk of harmful effects if used for the management of head injury or stroke.	Specific statement in section 4.4 of SmPC	NA
Risk of increased in mortality if therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS).	Specific statement in section 4.4 of SmPC	NA
Risk of neurodevelopmental adverse events in premature infants.	Specific statement in section 4.4 of SmPC	NA
Risk of adrenal cortical atrophy during prolonged therapy.	Specific statement in section 4.4 of SmPC	NA
Risk of withdrawal symptoms in case of withdrawal of a prolonged therapy	Specific statement in section 4.4 of SmPC	Patients in UK should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.
Risk of potential fatal infection in case of exposure to chickenpox.	Specific statement in section 4.4 of SmPC	Patients in UK should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.
Risk of severe infection in case of exposure to measles.	Specific statement in section 4.4 of SmPC	Patients in UK should carry 'Steroid treatment' cards which

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of abnormalities of foetal development e.g. cleft palate, intra-uterine growth retardation, brain growth and development	Specific statement in section 4.6 of SmPC	NA
Risk of hypoadrenalism in neonates	Specific statement in section 4.6 of SmPC	NA
No data on fertility are available for dexamethasone	Specific statement in section 4.6 of SmPC	NA
There are no data on dexamethasone during lactation	Specific statement in section 4.6 of SmPC	NA

The RMP for Dexamethasone 3.3 mg/ml Solution for Injection or Infusion adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of dexamethasone and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

IV.7 Discussion on the clinical aspects

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application.

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 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.*

V. OVERALL CONCLUSIONS

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5643/1/DC to IE/H/0609/1/DC			
MAH transfer				04/01/2021