IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dexamethasone Phosphate 1mg/ml (as sodium phosphate) Eye Drops Solution in a single dose container
DEXAMETHASONE PHOSPHATE
PA1339/052/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5556/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20/06/2018 under procedure number IE/H/0610/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: [PA1339/052/001
Marketing Authorisation Holder: Wockhardt UK Limited
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 phosphate Eye Drops (PL 29831/0589; UK/H/5556/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for treatment of non-infectious inflammatory conditions affecting the anterior segment of the eye.

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(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Dexafree 1mg/ml, eye drops, solution in a single-dose container which was originally granted in the Netherlands in 1996 (Thea Pharma NV; RVG 18658) and subsequently underwent a mutual recognition procedure (MRP) with Netherlands as RMS and Austria, Belgium, Bulgaria, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland (Dexafree 1 mg/ml, eye drops, solution PA 1107/005/001), Italy, Luxembourg, Norway, Poland, Portugal, Slovenia, Spain, Sweden and the United Kingdom (Dexafree 1 mg/ml, eye drops, solution PL 20162/0013) as concerned member states in 2012.

Dexamethasone sodium phosphate is a hydrosoluble inorganic ester of dexamethasone. It is a synthetic corticosteroid with an anti-inflammatory and anti-allergic action. Dexamethasone has more potent anti-inflammatory action compared to hydrocortisone (approximately 25:1) and prednisolone (approximately 5:1).

No new clinical or non-clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to an originator product that has been licensed for over 10 years. In accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) and the *Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents* (CPNP/EWP/239/95 final), bioequivalence and comparative clinical studies are not required and none were submitted.

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 210) on 24 November 2014. After a subsequent national phase, a licence was granted in the UK on 17 December 2014.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

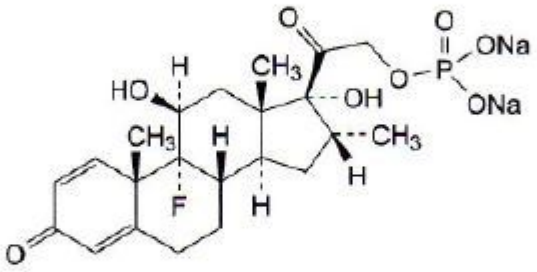
Each 1ml of solution contains 1mg of dexamethasone phosphate (as dexamethasone sodium phosphate). Each individual single-dose unit contains 0.4 mg dexamethasone phosphate (as dexamethasone sodium phosphate) in 0.4 ml of solution in the pharmaceutical form of eye drops, solution. Other ingredients consist of the pharmaceutical excipients sodium chloride, disodium edetate, disodium phosphate dodecahydrate (E339) and purified water. The finished product is packed into 0.4 ml transparent low density polyethylene (LDPE) single-dose units packaged in airtight pre-formable PET metal/PE transparent and PET metal/PE peelable sachet. Each sachet contains 5 single-dose units. Four sachets (20 single-dose units) are packed into one carton. 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-11β,17 dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21yl disodium phosphate.
Dexamethasone 21 fosfate sodium

Structural formula:



Molecular formula:	$C_{22}H_{28}FNa_2O_8P$
Molecular mass:	516.4 g/mol
Appearance:	A white or almost white, hygroscopic powder.
Solubility:	Freely soluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride.

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.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, eye drop, solution containing 1mg of dexamethasone phosphate (as dexamethasone sodium phosphate) per each ml of

solution that could be considered to be essentially similar to the reference product Dexafree 1mg/ml, eye drops, solution in a single-dose container (Thea Pharma NV).

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the proposed and originator product. In vitro equivalence of the proposed product to the originator product has been adequately demonstrated.

All excipients comply with their respective European Pharmacopoeia monographs. 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 36 months for the unopened sachet. After opening the sachet, the contents must be used within 28 days. After opening the single-dose container, the contents must be used immediately. Discard any unused contents. The storage conditions are 'Do not store above 25°C. Store in the original package.'

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.

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 phosphate Eye Drops 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 hybrid 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**) and the *Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents* (CPNP/EWP/239/95 final), bioequivalence studies were not conducted and none are required for this type of product.

No new clinical data were provided. The applicant has justified the grounds for a biowaiver for the need to provide equivalence data and this is accepted, on the basis that the product is an aqueous solution for topical use, with the same concentration of active substance and the same excipient profile as the reference 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 ocular dexamethasone.

IV.2 Pharmacokinetics

As per the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) and the *Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents* (CPNP/EWP/239/95 final), the test product is to be administered as an aqueous solution for topical use, with the same concentration of active substance and the same excipient profile as the reference 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 phosphate Eye Drops.

A summary of safety concerns as approved in the RMP is listed below:

Summary of safety concerns	
Important identified risks	- hypersensitivity to any of the ingredients - masking signs of infections (including viral, parasitic, bacterial and fungal infections) - perforation, ulceration and injury of cornea with uncompleted epithelialisation - known glucocorticosteroid-induced ocular hypertension
Important potential risks	- ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation, especially in children and elderly population associated with prolonged use. - Opportunist infections (impaired immune response) - patients with corneal ulcer - thinning of the cornea and sclera - corneal calcification requiring corneal graft surgery - adrenal suppression in children with long term use - Chronic use risks – cataracts - Use with contact lenses
Important missing information	- Interaction with ocular medication - Pregnancy, lactation and fertility

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity to any of the ingredients.	Routine risk minimisation. The SmPC is up to date. Section 4.3, Contraindications states 'Hypersensitivity to the active substance or any of the excipients listed in section 6.1.' Section 4.8, Undesirable effects - states – - Uncommon (≥1/1,000 to <1/100): Allergic and hypersensitivity reactions	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Masking signs of infections (including viral, parasitic, bacterial and fungal infections)	Routine risk minimisation. The SmPC is up to date. Section 4.3, Contraindications states – Eye infections not controlled by anti-infectious treatment, such as: • Acute purulent bacterial infections including Pseudomonas and mycobacterial infections, • Fungal infections, • Epithelial Herpes simplex keratitis (dendritic keratitis), vaccinia, varicella zoster and most other viral infections of the cornea and conjunctiva, • Amoebic Keratitis, Section 4.4, Special warnings and precautions for use states – Patients with an eye infection should only receive local steroid treatment when the infection has been controlled by an effective anti-infectious treatment. Such patients should be carefully and regularly monitored by an ophthalmologist.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Perforation, ulceration and injury of cornea with uncompleted epithelialisation	Routine risk minimisation. The SmPC is up to date. Section 4.3, Contraindications states – Perforation, ulceration and injury of cornea with uncompleted epithelialisation (see also section 4.4). Section 4.4, Special warnings and precautions for use states – Thinning of the cornea and sclera may increase the risk of perforations with the use of topical corticosteroids. Section 4.8 Undesirable effects, states – Very rare (<1/10,000, including isolated reports):	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Perforation Description of selected adverse reactions In diseases causing thinning of the cornea, topical use of steroids could lead to perforation in some cases.	
Known glucocorticosteroid-induced ocular hypertension.	Routine risk minimisation. The SmPC is up to date. Section 4.3, Contraindications states – Known glucocorticosteroid-induced ocular hypertension. Section 4.4, Special warnings and precautions for use states – Prolonged use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation, especially in children and elderly population Section 4.8 Undesirable effects, states – Description of selected adverse reactions Prolonged use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation, Children and elderly patients may be particularly susceptible to steroid-induced IOP rise.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation, especially in children and elderly population associated with prolonged use.	Routine risk minimisation. The SmPC is up to date. Section 4.4 Special warnings and precautions for use, states - Prolonged use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation, especially in children and elderly population. Section 4.8 Undesiarable effects states – - Uncommon (≥1/1,000 to <1/100): glaucoma*. Increase of the intra-ocular pressure, glaucoma and cataract may occur. Prolonged use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or Glaucoma) and also cataract formation,	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Children and elderly patients may be particularly susceptible to steroid-induced IOP rise.	
Opportunist infections (impaired immune response)	Routine risk minimisation. The SmPC is up to date. Section 4.4 Special warnings and precautions for use, states – The use of corticosteroids may also result in opportunistic ocular infections due to the suppression of host response or to the delay of their healing. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of opportunistic eye infections. Section 4.8 Undesirable effects, states – - Uncommon (≥1/1,000 to <1/100): opportunistic infections	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Patients with corneal ulcer	Routine risk minimisation. The SmPC is up to date. Section 4.4 Special warnings and precautions for use, states – Patients with a corneal ulcer should generally not receive topical dexamethasone except when inflammation is the main cause of healing delay and when the appropriate aetiological treatment has already been prescribed. Such patients should be carefully and regularly monitored by an ophthalmologist. Section 4.8 Undesirable effects, states - states – - Very rare (<1/10,000, including isolated reports): Corneal ulceration.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Thinning of the cornea and sclera	Routine risk minimisation. The SmPC is up to date. Section 4.4, Special warnings and precautions for use, states - Thinning of the cornea and sclera may increase the risk of perforations with the use of topical	No additional risk minimisation activities are necessary for the safe and

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	corticosteroids. Section 4.8, Undesirable effects, states – In diseases causing thinning of the cornea, topical use of steroids could lead to perforation in some cases.	effective use of the medicinal product.
Corneal calcification requiring corneal graft surgery	Routine risk minimisation. The SmPC is up to date. Section 4.4, Special warnings and precautions for use, states – Corneal calcification requiring corneal graft surgery for visual rehabilitation has been reported for patients treated with ophthalmic preparations containing phosphates such as Dexamethasone phosphate 1mg/ml eye drops. At the first sign of corneal calcification the drug should be withdrawn and the patient should be switched to a phosphate-free preparation. Section 4.8 Undesirable effects, states – - Very rare (<1/10,000, including isolated reports): Corneal calcifications.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Adrenal suppression in children with long term use	Routine risk minimisation. The SmPC is up to date. Section 4.2 Posology and method of administration, states – In children, long-term continuous corticosteroid therapy should be avoided due to possible adrenal suppression. Section 4.4, Special warnings and precautions for use, states – In children, long-term continuous corticosteroid therapy should be avoided due to possible adrenal suppression. Section 4.8, Undesirable effects, states – - Uncommon (≥1/1,000 to <1/100): Depression of adrenal function. Depression of adrenal function associated with systemic absorption of the product may occur when the instillations are administered with a frequent dosing schedule	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Chronic use risks – cataracts	Routine risk minimisation. The SmPC is up to date. Section 4.4, Special warnings and precautions for use, states – Posterior subcapsular cataract might occur at cumulative doses of dexamethasone. Diabetics are also more prone to develop subcapsular cataracts	No additional risk minimisation activities are necessary for the safe and effective use of

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	following topical steroid administration. Section 4.8 Undesirable effects, states – Diabetics are also more prone to develop subcapsular cataracts following topical steroid administration.	the medicinal product.
Use with contact lenses.	Routine risk minimisation. The SmPC is up to date. Section 4.4, Special warnings and precautions for use, states – Wearing of contact lenses during treatment with corticosteroid eye drops should be avoided.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Interaction with ocular medication	Routine risk minimisation. The SmPC is up to date. Section 4.5 Interaction with other medicinal products and other forms of interaction, states – No interaction studies have been performed. In case of concomitant treatment with other eye drops, solution, instillations should be spaced out by 15 minutes. Superficial stromal corneal precipitations of calcium phosphate have been reported under combined use of corticosteroids and topical beta-blockers.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.
Pregnancy, lactation and fertility	Routine risk minimisation. The SmPC is up to date. Section 4.6 Fertility, pregnancy and lactation states – Pregnancy Insufficient data are available on the use of Dexamethasone phosphate 1 mg/ml, eye drops, solution in single-dose container in human pregnancy to assess possible harmful effects. Corticosteroids cross the placenta. Teratogenic effects have been observed in animals (see section 5.3). However, there is no evidence to date that teratogenic effects are induced in humans. After systemic use of corticosteroids, at higher doses, effects on the unborn/neonate (intrauterine growth inhibition, inhibition of the function of the adrenal cortex) have been reported. However, these effects have not been reported for ocular use. As a precautionary measure, it is preferable to avoid the use of Dexamethasone 1 mg/ml, eye drops, solution in single-dose container during pregnancy.	No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Breastfeeding It is not known whether this medicine is excreted in breast milk. However the total dose of dexamethasone is low. Dexamethasone phosphate 1mg/ml (as sodium phosphate) Eye Drops, Solution in a single-dose container can be used during lactation. Fertility There are no data on potential effects of Dexamethasone 1 mg/ml on fertility.	

The RMP for Dexamethasone phosphate Eye Drops 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 hybrid 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 administered as aqueous solutions for topical use, with the same concentration of active substance and the same excipient profile.

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/5556/1/DC to IE/H/0610/1/DC			