Public Assessment Report

Decentralised Procedure

Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container

Procedure No: UK/H/5450/001/DC

UK Licence No: PL 30322/0001

Alissa Healthcare Research Limited

Medicines and Healthcare Products Regulatory Agency

Lay Summary

Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container
(dexamethasone phosphate, as dexamethasone sodium phosphate)

This is a summary of the public assessment report (PAR) for Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container (PL 30322/0001; UK/H/5450/001/DC). Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container will be referred to as Dexamethasone phosphate 1 mg/ml eye drops throughout this report, for ease of reading. It explains how Dexamethasone phosphate 1 mg/ml eye drops were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Dexamethasone phosphate 1 mg/ml eye drops.

For practical information about using Dexamethasone phosphate 1 mg/ml eye drops, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone phosphate 1 mg/ml eye drops and what are they used for?
Dexamethasone phosphate 1 mg/ml eye drops are a 'hybrid generic medicine'. This means that they are similar to a reference medicine containing the same active substance, already authorised in the European Union (EU), called Dexafree 1 mg/ml, eye drops, solution.

Dexamethasone phosphate 1 mg/ml eye drops are used to treat inflammatory conditions affecting the front part of the eye that are not caused by infections.

How do Dexamethasone phosphate 1 mg/ml eye drops work?
Dexamethasone phosphate 1 mg/ml eye drops contain the active substance dexamethasone phosphate (as dexamethasone phosphate monohydrate). Dexamethasone phosphate works by inhibiting a particular enzyme, thereby preventing the generation of substances which cause inflammation.

How are Dexamethasone phosphate 1 mg/ml eye drops used?
Dexamethasone phosphate 1 mg/ml eye drops should be used in the eye (ocular use). The usual dose is 1 drop, 4 to 6 times a day in the eye to be treated. If the condition is more serious, the patient may be instructed to start with 1 drop every hour and then change to 1 drop every 4 hours, after the medicine has started to work. It is important to reduce the dose gradually in order to avoid the condition worsening again, once the medication is stopped.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription.

How have Dexamethasone phosphate 1 mg/ml eye drops been studied?
Because Dexamethasone phosphate 1 mg/ml eye drops are a hybrid application and are considered to be therapeutically equivalent to the reference product Dexafree 1 mg/ml, eye drops, solution, their benefits and risks are taken as being the same as those of the reference medicine.

What are the possible side effects of Dexamethasone phosphate 1 mg/ml eye drops?
The most common side effect with Dexamethasone phosphate 1 mg/ml eye drops (which may affect more than 1 in 10 people) is an increase pressure in the eye.

The most common side effects with Dexamethasone phosphate 1 mg/ml eye drops (which may affect up to 1 in 10 people) are discomfort, irritation, burning, stinging, itching and blurred vision after use. These do not usually last long.

For a full list of restrictions, see the package leaflet.

Why are Dexamethasone phosphate 1 mg/ml eye drops approved?
It was decided that the benefits of Dexamethasone phosphate 1 mg/ml eye drops outweigh the identified risks and it was recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Dexamethasone phosphate 1 mg/ml eye drops?
A Risk Management Plan (RMP) has been developed to ensure that Dexamethasone phosphate 1 mg/ml eye drops are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Dexamethasone phosphate 1 mg/ml eye drops, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Dexamethasone phosphate 1 mg/ml eye drops
Ireland and the UK agreed to grant a marketing authorisation to Alissa Healthcare Research Limited for Dexamethasone phosphate 1 mg/ml eye drops on 13 January 2015. The marketing authorisation in the UK was granted on 29 January 2015.

The full PAR for Dexamethasone phosphate 1 mg/ml eye drops follows this summary.

For more information about treatment with Dexamethasone phosphate 1 mg/ml eye drops, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to Alissa Healthcare Research Limited for the medicinal product Dexamethasone phosphate 1 mg/ml eye drops.

This product is a prescription-only medicine (legal status POM), indicated for the treatment of non-infectious inflammatory conditions affecting the anterior segment of the eye.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as a Concerned Member States (CMS). The application was made under Article 10(3) of Directive 2001/83/EC, as amended, as a 'hybrid' application. The reference medicinal product, which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area (EEA), is Monofree Dexamethason 1mg/ml; this product was authorised to Thea Pharma NV in the Netherlands on 17 September 1996. This licence subsequently underwent a Mutual Recognition (MR) procedure (NL/H/653/001), which was approved on 27 October 2005. Following a further MR Repeat-Use Procedure (RUP), this product was recognised in the UK and an MA was granted to Laboratoires Thea on 19 September 2012 (PL 20162/0013). Within this report the reference product will be referred to by the UK product name, Dexafree 1 mg/ml eye drops, solution.

Dexamethasone is a highly potent and long-acting glucocorticoid. It has an approximately seven times greater anti-inflammatory potency than prednisolone, another commonly prescribed corticosteroid. The actions of corticosteroids are mediated by the binding of the corticosteroid molecules to receptor molecules located within sensitive cells. Corticosteroid receptors are present in human trabecular meshwork cells and in rabbit iris ciliary body tissue.

Corticosteroids will inhibit phospholipase A2, thereby preventing the generation of substances which mediate inflammation, for example, prostaglandins. Corticosteroids also produce a marked, though transient, lymphocytopenia. This depletion is due to redistribution of the cells, the T lymphocytes being affected to a greater degree than the B lymphocytes. Lymphokine production is reduced, as is the sensitivity of macrophages to activation by lymphokines. Corticosteroids also retard epithelial regeneration, diminish post-inflammatory neo-vascularisation, and reduce, towards normal levels, the excessive permeability of inflamed capillaries.

The application for Dexamethasone phosphate 1 mg/ml eye drops was submitted as a hybrid application. Since the product is intended for topical application, is locally applied and is intended for local action, plasma pharmacokinetic studies to establish bioequivalence are not suitable and, therefore, clinical studies of therapeutic equivalence are, in principle, necessary (CPMP/EWP/239/95 final). A waiver of the need to provide clinical equivalence data was requested by the MA holder, based on the fact that the active substance in Dexamethasone phosphate 1 mg/ml eye drops is dissolved and of equal concentration to the active substance in the reference product. Sufficient data was provided to support this biowaiver and, therefore, no new clinical studies were required. This is in line 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* (CPMP/EWP/239/95 final).

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

Since Dexamethasone phosphate 1 mg/ml eye drops are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type 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.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 13 January 2015. After a subsequent national phase, a licence was granted in the UK on 29 January 2015.

II Quality aspects

II.1 Introduction

The application is submitted according to Article 10(3) of Directive 2001/83/EC, as amended. The applicant has specified Dexafree 1 mg/ml eye drops, solution as the reference medicinal product.

Dexamethasone phosphate 1 mg/ml eye drops are formulated as a colourless solution, when examined under suitable conditions of visibility, and practically clear and free from particles. Dexamethasone phosphate 1 mg/ml eye drops are manufactured as single-use, unpreserved sterile eye drops.

Each 1 ml of the eye drops solution contains 1 mg of the active substance dexamethasone phosphate, as dexamethasone sodium phosphate. The excipients present are: sodium chloride, sodium edetate, disodium phosphate dodecahydrate (E339) and purified water.

Dexamethasone phosphate 1 mg/ml eye drops are packaged in transparent low density polyethylene (LDPE) single-dose units in peelable polyester/aluminium/polyethylene sachets. Each single dose unit contains 0.4 ml solution and there are five single dose units in each sachet, which are further packed into cartons. Each carton contains four sachets.

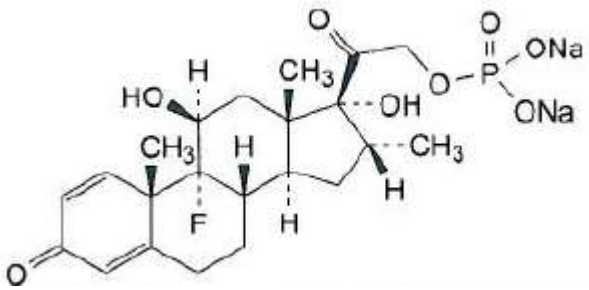
II.2 Drug Substance

Dexamethasone sodium phosphate

INN: Dexamethasone sodium phosphate

Chemical Name: 9-Fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate.

Structure:



Molecular formula: $C_{22}H_{28}FNa_2O_8P$

Molecular weight: 516.4 g/mol

Appearance: A white or almost white, very hygroscopic powder. The drug substance shows polymorphism.

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 a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical development

The objective was to develop a product equivalent to the reference product Dexafree 1 mg/ml eye drops, solution in a single dose container.

The development of the product has been adequately described.

As this product provides local therapeutic, and not systemic, activity, investigation of bioequivalence is not appropriate for this product as per "*Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents"* (CPMP/EWP/239/95 final) and the "*Guideline on the Investigation of Bioequivalence*" (CPMP/EWP/QWP/1401/98 Rev.1) Appendix II. Bioequivalence is based on the comparability of the physico-chemical characteristics between this product and the reference product.

Comparative physico-chemical analysis between three batches of Dexamethasone phosphate 1 mg/ml eye drops and three batches of reference medicinal product, Dexafree 1 mg/ml eye drops, solution, was undertaken. Statistical evaluation of the data has been performed and results show that there is no significant difference in the reported physicochemical parameters of test and reference product batches. This is discussed further in Section IV – Clinical aspects.

All the excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeia monographs.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

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 finished product, together with an appropriate description of the manufacturing process. Satisfactory process validation was performed for the manufacturing process on three production-scale validation batches.

Product Specifications

The finished product specification is satisfactory. Satisfactory batch analysis was performed on three production-scale batches of the finished product. Certificates of analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed in accordance with current guidelines on three batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for an unopened sachet and 28 days once the sachet is opened. After opening of the single-dose unit the product should be used immediately and any unused content should be discarded. The following storage conditions apply: do not store above 25°C; store in the original package in order to protect from light; do not refrigerate or freeze; and, discard any remaining single-dose units 28 days after opening the sachet.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III Non-clinical aspects

No new non-clinical studies have been submitted in support of this application. The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known. As dexamethasone is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. A satisfactory non-clinical overview, based on a review of the literature, has been supplied.

There are no objections to approval of Dexamethasone phosphate 1 mg/ml eye drops from a non-clinical point of view.

Environmental Risk Assessment (ERA)

Since Dexamethasone phosphate 1 mg/ml eye drops are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

IV Clinical aspects

IV.1 Introduction

The application has been submitted under Article 10(3) according to Directive 2001/83/EC, as amended. The applicant sought a biowaver of clinical studies and this was accepted – please see Sections II.3 and IV.2. No new clinical data was, therefore, required for this application and none were submitted.

The applicant's clinical overview has been written by a suitably qualified person and provides an adequate summary of published literature on the clinical pharmacology, efficacy and safety of ocular dexamethasone. This is considered acceptable.

IV.2 Pharmacokinetics

No clinical studies have been conducted to support the application. Dexamethasone phosphate 1 mg/ml eye drops and the reference product, Dexafree 1 mg/ml eye drops solution, are both intended for topical application, both locally applied and both intended for local action. The active substance in Dexamethasone phosphate 1 mg/ml eye drops is dissolved and of equal concentration to the active substance in the reference product.

Essential similarity is based on the comparability of the physico-chemical characteristics between this product and the reference product. Comparative physicochemical analysis between Dexamethasone phosphate 1 mg/ml eye drops and the reference medicinal product, Dexafree 1 mg/ml eye drops solution, has demonstrated pharmaceutical equivalence of a sufficient degree to infer therapeutic equivalence and, therefore, clinical interchangeability between the proposed and reference product. (Please see Section II.3 for details on the comparative analysis).

IV.3 Pharmacodynamics

A biowaver has been accepted for this application and, therefore, no new pharmacodynamics data are required and none have been submitted. The applicant's review of the literature in the clinical overview is acceptable.

IV.4 Clinical efficacy

A biowaver has been accepted for this application and, therefore, no new clinical efficacy data are required and none have been submitted. The applicant's review of the literature in the clinical overview is acceptable.

IV.5 Clinical safety

A biowaver has been accepted for this application and, therefore, no new clinical safety data are required and none have been submitted. The applicant's review of the literature in the clinical overview is acceptable.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an 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 1 mg/ml eye drops.

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

Summary table of safety concerns

Important identified risks	• Hypersensitivity to any ingredients • Eye infections such as acute purulent bacterial infections, epithelial Herpes simplex and other viral diseases, fungal infection, Amoebic keratitis and undiagnosed red eye. • Adrenal suppression (associated with long term use in children) • Glaucoma and perforation, ulceration of the cornea with uncompleted epithelialisation • Patients with/previously has glucocorticosteroid-induced ocular hypertension
Important potential risks	• Risk of opportunistic infection, aggravation or making of signs of infection, cataracts and delayed wound healing • Corneal deposits or opacity including possible interaction with other phosphate containing medicines • Concomitant use of topical beta-blocker • Blurred vision • Concomitant use with contact lenses
Important missing information	• Use in pregnancy and/or lactation

Planned risk minimisation activities

Safety Concern	Routine Risk minimisation	Additional risk minimisation
Hypersensitivity to any ingredients	Proposed text in SPC section 4.3 'Contraindications' states: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.	None proposed
Eye infections such as acute purulent bacterial infections, epithelial Herpes simplex and other viral diseases, fungal infection, Amoebic keratitis and undiagnosed red eye.	Proposed text in SPC section 4.3 'Contraindications'; section 4.4' Special warnings and precautions for use' state: 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. Topical steroids should never be given for an undiagnosed red eye.	None proposed
Adrenal suppression (associated with long term use in children)	Proposed text in SPC section 4.2 'Posology and method of administration' section 4.4' Special	None proposed

Safety Concern	Routine Risk minimisation	Additional risk minimisation
	warnings and precautions for use' state: In children, long-term continuous corticosteroid therapy should be avoided due to possible adrenal suppression (see section 4.4). .	
Glaucoma and perforation, ulceration of the cornea with uncompleted epithelialisation	Proposed text in SPC section 4.3 'Contraindications' section 4.4' Special warnings and precautions for use' state: Perforation, ulceration and injury of cornea with uncompleted epithelialisation (see also sections 4.4). 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. Thinning of the cornea and sclera may increase the risk of perforations with the use of topical corticosteroids. Patients should be monitored at frequent intervals during treatment with dexamethasone eye drops. 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.	None proposed
Patients with/previously had glucocorticosteroid-induced ocular hypertension	Proposed text in SPC section 4.3 'Contraindications' section 4.4' Special warnings and precautions for use' state: Known glucocorticosteroid-induced ocular hypertension. Patients should be monitored at frequent intervals during treatment with dexamethasone eye drops. 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.	None proposed
Risk of opportunistic infection, aggravation or masking of signs of infection, cataracts and delayed wound healing	Proposed text in SPC section 4.4' Special warnings and precautions for use' state: 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. Posterior subcapsular cataract might occur at cumulative doses of dexamethasone.	None proposed
Corneal deposits or opacity including possible interaction with other phosphate containing	Proposed text in SPC section 4.4' Special warnings and precautions for use' state: Corneal calcification requiring corneal graft	None proposed

Safety Concern	Routine Risk minimisation	Additional risk minimisation
medicines	surgery for visual rehabilitation has been reported for patients treated with ophthalmic preparations containing phosphates such as Dexamethasone 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.	
Concomitant use of topical beta-blocker	Proposed text in SPC section 4.5 'Interactions with other medicinal products and other forms of interaction' states: Superficial stromal corneal precipitations of calcium phosphate have been reported under combined use of corticosteroids and topical beta-blockers.	None proposed
Blurred vision	Proposed text in SPC section 4.7 'Effects on the ability to drive and use machines' states: As with any eye drops, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.	None proposed
Concomitant use with contact lenses	Proposed text in SPC section 4.4' Special warnings and precautions for use' state: Wearing of contact lenses during treatment with corticosteroid eye drops should be avoided.	None proposed
Use in pregnancy and/or lactation	Proposed text in SPC section 4.6 'Fertility, Pregnancy and lactation' states: Pregnancy Insufficient data are available on the use of Dexamethasone 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. Breastfeeding It is not known whether this medicine is excreted in breast milk. However the total dose of dexamethasone is low. Dexamethasone 1 mg/ml eye drops, solution in single-dose container can be used during lactation. Fertility There are no data on potential effects of Dexamethasone 1 mg/ml on fertility.	None proposed

V.7 Discussion on the clinical aspects

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, as amended. The language used for the purpose of user testing the package leaflet 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*.

VI Overall conclusion, benefit/risk assessment and recommendation

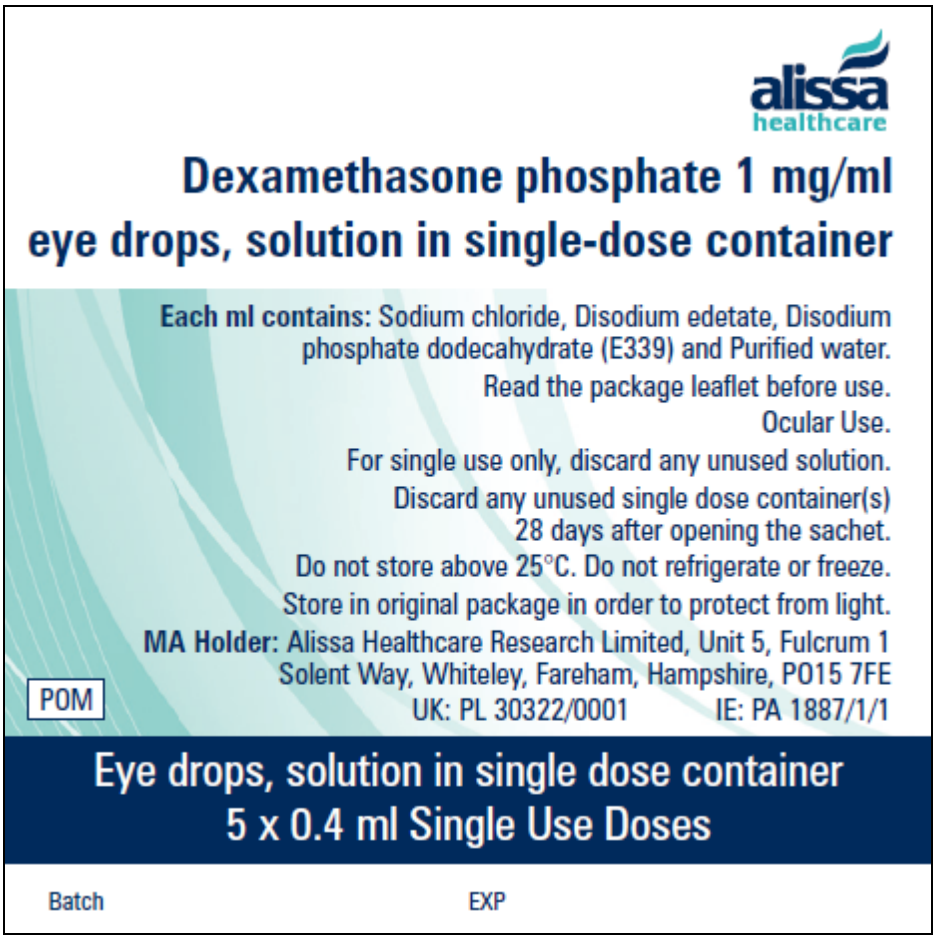
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The application for Dexamethasone phosphate 1 mg/ml eye drops solution is a hybrid version of a well-established reference product, Dexafree 1 mg/ml eye drops solution. For hybrid versions of products that are locally applied and intended for local action, clinical studies of therapeutic equivalence are generally required as plasma pharmacokinetic analysis is unable to provide evidence of bioequivalence (CPMP/EWP/239/95 final). In this application, a waiver of clinical equivalence studies was sought on the basis that the active substance is present in solution and at the same concentration in the test and reference products. The applicant provided data to demonstrate a sufficient degree of pharmaceutical equivalence from which therapeutic equivalence can be inferred.

The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labels are listed below:



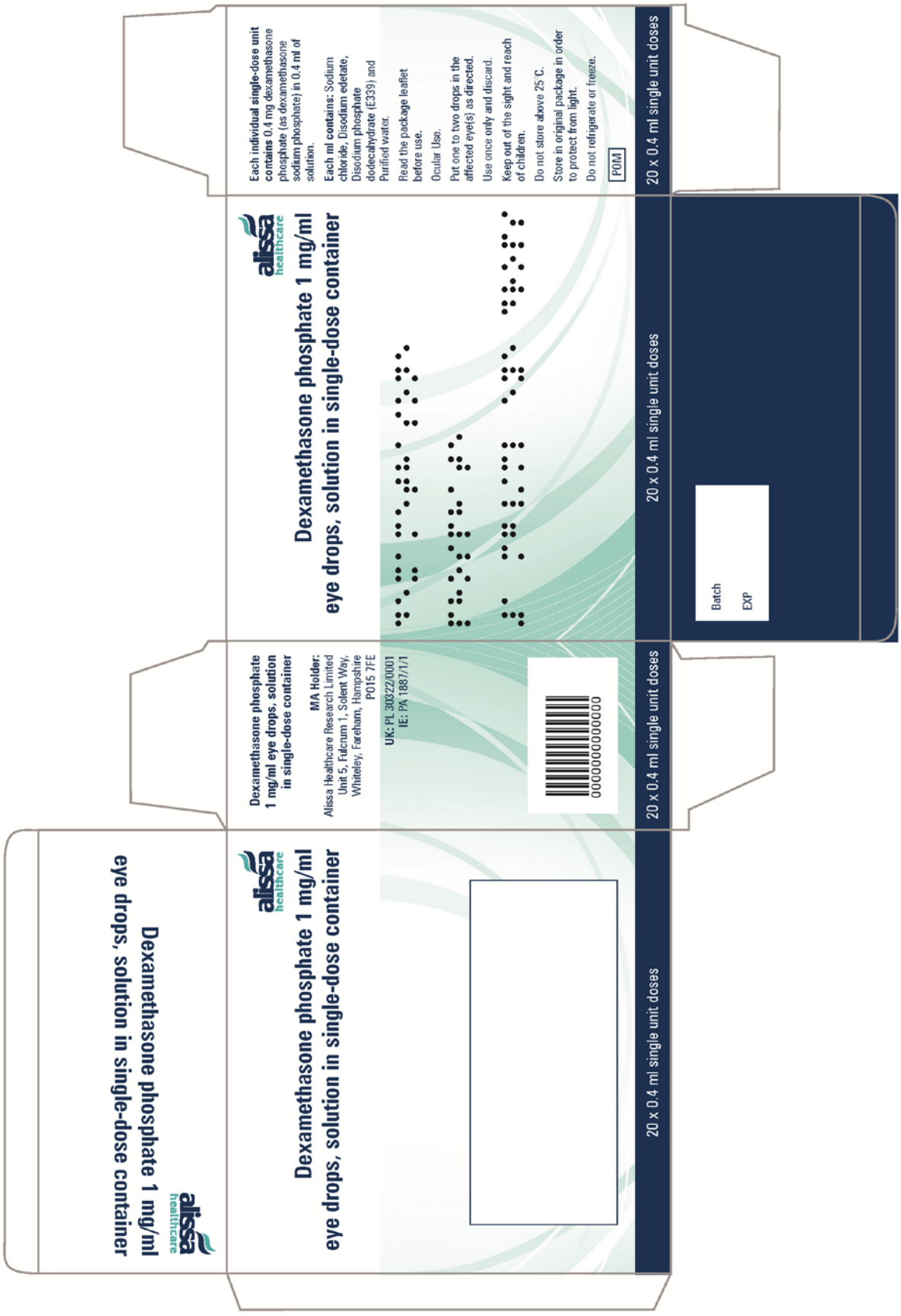

alissa healthcare
Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container
20 x 0.4 ml single unit doses
Dexamethasone phosphate 1 mg/ml eye drops, solution in single-dose container
MA Holder:
Alissa Healthcare Research Limited
Unit 5, Fulcrum 1, Solent Way,
Whiteley, Fareham, Hampshire
PO15 7FE
UK: PL 30322/0001
IE: PA 1887/1/1
00000000000
Each individual single-dose unit contains 0.4 mg dexamethasone phosphate (as dexamethasone sodium phosphate) in 0.4 ml of solution.
Each ml contains: Sodium chloride, Disodium edetate, Disodium phosphate dodecahydrate (E339) and Purified water.
Read the package leaflet before use.
Ocular Use.
Put one to two drops in the affected eye(s) as directed.
Use once only and discard.
Keep out of the sight and reach of children.
Do not store above 25°C.
Store in original package in order to protect from light.
Do not refrigerate or freeze.
POM
Batch
EXP

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)