Public Assessment Report

Decentralised Procedure

Eykappo 5 mg/ml eye drops solution

(chloramphenicol)

Procedure No: UK/H/6007/001/DC

UK Licence No: PL 35533/0123

Aspire Pharma Limited
LAY SUMMARY
Eykappo 5 mg/ml eye drops solution
(chloramphenicol)

This is a summary of the Public Assessment Report (PAR) for Eykappo 5 mg/ml eye drops solution (PL 35533/0123; UK/H/6007/001/DC). It explains how Eykappo 5 mg/ml eye drops solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Eykappo 5 mg/ml eye drops solution.

This product will be referred to as Eykappo 5 mg/ml eye drops solution in this lay summary for ease of reading.

For practical information about using Eykappo 5 mg/ml eye drops solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Eykappo 5 mg/ml eye drops solution and what is it used for?
Eykappo 5 mg/ml eye drops solution is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Eykappo 5 mg/ml eye drops solution has been in well-established use in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Eykappo 5 mg/ml eye drops solution is a sterile solution with no preservatives used to treat infections of the eyes.

If the eye infection is very severe, a doctor may give patients antibiotic tablets as well as this antibiotic eye drops.

How do Eykappo 5 mg/ml eye drops solution work?
Eykappo 5 mg/ml eye drops solution contains a medicine called chloramphenicol. This belongs to a group of medicines called antibiotics. This medicine treats infections of the outer surface of the eye, such as the cornea (the transparent membrane covering the surface of the eye) or the conjunctiva (the lining of the inside of the eyelids and part of the eye) caused by bacteria.

How are Eykappo 5 mg/ml eye drops solution used?
Eykappo 5 mg/ml eye drops solution is for use in the eye (ocular use).

This product must not be used for longer than the time frame stated by a doctor or eye specialist, as it may become less effective at treating eye infection.

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

The recommended dose in adults and the elderly is 1 to 2 drops to each infected eye up to six times a day. The patient must continue with the treatment for 2 days after symptoms disappear to prevent the recurrence of infection. The maximum recommended duration of treatment is 14 days.

Patients should see the doctor, eye specialist or pharmacist if the eyes get worse or are not better after a few days of using these eye drops.

Use in children
It may be necessary to adjust the dose for newborn infants as, due to their immature metabolism they may be at risk of dose-related adverse effects. The maximum duration of treatment is 10-14 days.

The tip of the multi dose container should not touch the eye or areas around the eye as this can cause
injury to the eye. The eye drops solution may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision.

To avoid possible contamination of the multi-dose container, keep the tip of the multi-dose container away from contact with any surface.

This medicine can only be obtained with a prescription.

For further information on how Eykappo 5 mg/ml eye drops solution are used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet available on the MHRA website.

**What benefits of Eykappo 5 mg/ml eye drops solution have been shown in studies?**
As chloramphenicol is a well-known substance, and its use in the treatment of infections of the eyes is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of chloramphenicol for the proposed indication.

**What are the possible side effects of Eykappo 5 mg/ml eye drops solution?**
Like all medicines, Eykappo 5 mg/ml eye drops solution can cause side effects, although not everybody gets them.

For information about side effects that may occur with taking Eykappo 5 mg/ml eye drops solution, please refer to the package leaflet or the Summary of Product Characteristics available on the MHRA website.

**Why has Eykappo 5 mg/ml eye drops solution approved?**
The use of chloramphenicol in the treatment of infections of the eyes is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Eykappo 5 mg/ml eye drops solution outweigh the risks and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Eykappo 5 mg/ml eye drops solution?**
A Risk Management Plan has been developed to ensure that Eykappo 5 mg/ml eye drops solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Eykappo 5 mg/ml eye drops solution, 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/healthcare professionals will be monitored/reviewed continuously.

**Other information about Eykappo 5 mg/ml eye drops solution**
Denmark, Finland, Greece, Norway, Sweden and the UK agreed to grant a Marketing Authorisation for Eykappo 5 mg/ml eye drops solution on 01 February 2017. A Marketing Authorisation was granted in the UK to Pharmathen S.A., (PL 17277/0349) on 28 February 2017.

A change of ownership was granted on 22 March 2017, to change the Marketing Authorisation Holder to Aspire Pharma Limited (PL 35533/0123).

The full PAR for Eykappo 5 mg/ml eye drops solution follows this summary.

This summary was last updated in February 2018.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Eykappo 5 mg/ml eye drops solution (PL 35533/0123; UK/H/6007/001/DC), is approvable. This is a prescription-only medicine (POM), indicated in adults and children for the treatment of acute bacterial conjunctivitis. Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Denmark, Finland, Greece, Norway and Sweden as Concerned Member States (CMS). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Chloramphenicol is an antibiotic which is mainly bacteriostatic in action, but exerts a bactericidal effect against some strains of gram-positive cocci and against Haemophilus influenzae and Neisseria. It has a broad spectrum of action against both gram-positive and gram-negative bacteria, rickettsiae and chlamydia.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing active substances of well-established use.

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

The RMS has been assured that acceptable standards of Good Manufacturing Practice 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.

The Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 01 February 2017). Following a national phase, the UK granted a Marketing Authorisation (PL 17277/0349) for this product on 28 February 2017.

A Marketing Authorisation was originally granted to Pharmathen S.A., (PL 17277/0349) on 28 February 2017. Following a change of ownership procedure on 22 March 2017, the above product is currently licenced to Aspire Pharma Limited (PL 35533/0123).
II  QUALITY ASPECTS
II.1  Introduction
The finished product is an eye drop solution and contains 5 mg/ml chloramphenicol, as active ingredients. The excipients present in this product are boric acid, borax and sodium hydroxide or/and hydrochloric acid (for pH adjustment), and water for injection.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

No materials of animal or human origin are included in this product.

The finished product is presented as a clear, colourless aqueous solution in a white opaque low density polyethylene (LDPE) bottle and white Novelia nozzle (high density polyethylene and silicone) with a white HDPE cap. Each bottle is packaged in a cardboard.

II.2  Drug Substance
INN: Chloramphenicol
Chemical name(s): [R-(R*,R*)]-2,2-Dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide

2,2-Dichloro-N-[(1R,2R)-2-hydroxy-1- (hydroxymethyl) -2-(4-nitrophenyl)ethyl] acetamide.


Structure:

Molecular formula: C_{11}H_{12}Cl_{2}N_{2}O_{5}
Molecular weight: 323.1 g/mol
Appearance: White to yellowish crystalline powder.
Solubility: Freely soluble in ethyl alcohol and in propylene glycol. Slightly soluble in water and in ether.

Chloramphenicol is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been
appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The aim of the development programme was to formulate a stable ophthalmic solution free of preservatives that is qualitatively similar in composition and comparable in performance to the marketed products Optrex Infected Eye Drops (PL 00062/0051; Optrex Ltd) or Brochlor Eye drops (PL 04425/0366; Sanofi-Aventis).

The drug product composition is qualitatively the same and quantitatively very similar to the UK innovator product, Minims Chloramphenicol eye drops and equivalence, on quality grounds, has been demonstrated between the proposed product and Minims Chloramphenicol eye drops.

The medicinal product does not contain antimicrobial preservative and is packaged in the Novelia® multidose container. The Novelia container includes specially designed components and has been demonstrated to prevent microbiological contamination of the contents after opening and maintain appropriate microbiological quality of dispensed drops during use by patients, in accordance with European Pharmacopoeia requirements.

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 and has shown satisfactory results. Process validation data on full scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with storage conditions “Store between 2° and 8°C”, “Do not freeze” “and “Protect from light” have been set. Once the container is opened the product must be used within 28 days. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of chloramphenicol are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical literature data on the pharmacology, pharmacokinetics and toxicology of chloramphenicol.

### III.1 Pharmacology
Not applicable, see Section III.1 Introduction, above.

### III.2 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

### III.3 Toxicology
Not applicable, see Section III.1 Introduction, above.

### III.4 Ecotoxicity/Environmental Risk Assessment (ERA)
Since Eykappo 5 mg/ml eye drops solution are intended to substitute existing chloramphenicol eye drop products, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.5 Discussion of the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

### IV  CLINICAL ASPECTS

#### IV.1 Introduction
Chloramphenicol is well-established active substance. The details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

#### IV.2 BCS Biowaiver
According to the relevant EU Guidelines: [CPMP/EWP/QWP/1401/98 Rev. 1/Corr* and CPMP/EWP/4151/00 rev 1, CPMP/EWP/239/95], for an aqueous topical product with qualitatively and quantitatively the same active ingredients as has been previously approved, the need for equivalence data may be waived. Minor differences in excipients may be acceptable if the relevant pharmaceutical properties of the test and reference product are identical or essentially similar.

The Applicant has confirmed that the proposed chloramphenicol formulation fulfils these biowaiver criteria.

#### IV.3 Pharmacokinetics
The pharmacokinetics (PK) of chloramphenicol are well recognised and relevant literature data have been presented in the Clinical Overview and Module 5.

#### IV.4 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted. Relevant literature data on the pharmacology of chloramphenicol have been presented in the Clinical Overview and Module 5.

#### IV.5 Clinical efficacy
The efficacy of chloramphenicol is well recognised. No new studies have been conducted. The efficacy of 0.5% chloramphenicol eye drops in the treatment of superficial eye infections is well established and was supported by appropriate bibliography.

IV.6 Clinical safety
The safety of chloramphenicol is well recognised. No new studies have been conducted. The safety of 0.5% chloramphenicol eye drops in the treatment of superficial eye infections is well established and the was supported by appropriate bibliography.

IV.7 Risk Management Plan (RMP)
The Marketing Authorisation Holder 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 Eykappo 5 mg/ml eye drops solution.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimization measures</th>
<th>Additional minimization measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions sensitivity</td>
<td><em>SmPC</em> section 4.3 Hypersensitivity to the active substance or to any component of the excipients listed in section 6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>section 4.8 Local Sensitivity reactions such as transient irritation, burning, stinging, itching and dermatitis, may occur.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIL sections 2 and 4 Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Bone marrow depression</td>
<td><em>No reference exists in proposed SmPC</em></td>
<td>None proposed</td>
</tr>
<tr>
<td>Condition</td>
<td>PIL Instruction</td>
<td>Relevance</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Aplastic Anaemia</td>
<td>No reference exists in proposed PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypersensitivity to chloramphenicol or any other component</td>
<td>No reference exists in proposed SmPC section 4.3 Hypersensitivity to the active substance or to any component of the preparation listed in section 6.1 PIL sections 2 and 4 Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>SmPC section 4.4 Prolonged use should be avoided as it may increase the likelihood of sensitisation and the emergence of resistant organisms PIL section 3 Do not use this product for longer than the time frame stated by your doctor or eye specialist, as it may become less effective at treating your eye infection</td>
<td>None proposed</td>
</tr>
<tr>
<td>Drug Sensitisation</td>
<td>SmPC section 4.4 Prolonged use should be avoided as it may increase the likelihood of sensitisation and the emergence of resistant organisms PIL section 2 Prescription only medicine</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
| No adequate and well controlled studies in pregnant and breastfeeding women | **SmPC** section 4.6  
**Pregnancy and Lactation**  
Safety for use in pregnancy and lactation has not been established, therefore, use only when considered essential by the physician  
**PIL section 2**  
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. The drops should not be used during pregnancy and breast-feeding unless considered essential by your doctor. | None proposed |
|---|---|---|
| Eye infection or injury | **SmPC** Section 4.2  
Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.  
Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.  
**PIL section 3**  
Do not allow the tip of the multi dose container to touch the eye or areas around the eye. It could cause injury to your eye. The eye drops solution may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision.  
To avoid possible contamination of the multi-dose container, keep the tip of the multi-dose container away from contact with any surface. | None proposed |
| Medication error | Routine risk minimisation activities. Information on correct handling of the | None proposed |
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.8 Discussion on the clinical aspects**

The grant of a Marketing Authorisation is recommended.

**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 patient information leaflet (PIL) was English.

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 concerns have been identified. The proposed product is in line with the brand leader and appropriate bibliographic references have been provided. Extensive clinical experience with chloramphenicol is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling is listed below:
PAR Eykappo 5 mg/ml eye drops solution

Eykappo
5 mg/ml
eye drops solution
chloramphenicol
10ml

Ocular use
Read the package leaflet before use.
Discard 4 weeks after first opening.

Opened:

PL 35533/0123
XXXXXX-1.1

UK/H/6007/001/DC
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)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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