Public Assessment Report

UKPAR

Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops)
(Sodium cromoglicate 2.0% w/v)

UK Licence No: PL 35533/0084

Aspire Pharma Limited.
LAY SUMMARY

Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops)

This is a summary of the Public Assessment Report (PAR) for Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops) (PL 35533/0084). It explains how Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops) was assessed and its authorisation recommended, as well as its condition of use. It is not intended to provide practical advice on how to use Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops).

The product will be collectively referred to as Sodium Cromoglicate throughout the remainder of this public assessment report.

For practical information about using Sodium Cromoglicate patients should read the package leaflet or contact their doctor or pharmacist.

What is Sodium Cromoglicate and what is it used for?
Sodium Cromoglicate is a ‘hybrid generic medicine’. This means that Sodium Cromoglicate is similar to a ‘reference medicine’ containing the same active substance already authorised in the UK called Opticrom Allergy 2.0% w/v Eye Drops, Solution (Aventis Pharma Limited).

Sodium Cromoglicate belongs to a group of medicines called anti-allergics and is used to treat allergic reactions. This medicine is used for the prevention and treatment of eye allergies. This type of allergy can happen at any time of the year and is referred to as ‘perennial allergic conjunctivitis’ or this can happen in different seasons of the year, caused by different pollens and is called ‘seasonal allergic conjunctivitis’ or hay fever.

How does Sodium Cromoglicate work?
This medicine contains the active ingredient called sodium cromoglicate, which works by stopping the release of the natural substances in the patient’s eyes that can lead to an allergic reaction. Signs of an allergic reaction include itchy, watery, red or inflamed eyes and puffy eyelids.

How is Sodium Cromoglicate used?
The pharmaceutical form of this medicine is an eye drop, solution, and the product is for use in the eye(s) (ocular use).

The patient should always use this medicine exactly as described in the package leaflet or as their doctor or pharmacist has advised. If unsure, the patient should ask the doctor or pharmacist.

This medicine also contains 0.1 mg benzalkonium chloride in each ml of solution, which may be absorbed by soft contact lenses and may change the colour of the contact lenses. The patient must remove contact lenses before using this medicine and put them back fifteen minutes afterwards.

Benzalkonium chloride may also cause eye irritation, especially if the patient has dry eyes or disorders of the cornea (the clear layer at the front of the eye). If the patient feels abnormal eye sensation, stinging or pain in the eye after using this medicine, they should talk to their doctor.

How much to use
- One or two drops in each eye four times a day, or as directed by the patient’s doctor.
If the patient’s symptoms worsen or do not improve, the patient must speak to their doctor or pharmacist.

**How to use this medicine**

- The patient must wash their hands
- Before using the medication for the first time, the patient must be sure that the tamper-proof seal on the bottle neck is unbroken. A gap between the bottle and the cap is normal for an unopened bottle
- Remove the cap from the bottle
- The patient must tilt their head back
- The patient must squeeze one or two drops inside the lower lid without touching their eye
- The patient must then close their eye
- Wipe away any excess liquid from their eyes with a clean tissue
- The patient must always put the cap back on the bottle as soon as they have used the bottle
- The patient can repeat the above process, in the other eye if needed

The patient should continue using these drops if they are still exposed to the substances(s) that they are allergic to. If the patient stops using this medicine their allergy symptoms may come back.

This medicine can be obtained without a prescription.

For further information on how to use Sodium Cromoglicate see section 3 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website

**What benefits of Sodium Cromoglicate have been shown in studies?**
Because Sodium Cromoglicate is considered to be therapeutically equivalent, to the reference product Opticrom Allergy 2.0% w/v Eye Drops, Solution (Aventis Pharma Limited), its benefits and risks are taken as being the same as those of the reference medicine.

**What are the possible side effects from Sodium Cromoglicate?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For a full list of all the side effects reported with Sodium Cromoglicate see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

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

**Why was Sodium Cromoglicate approved?**
The MHRA decided that the benefits of Sodium Cromoglicate are greater than the risks and recommended that the eye drops are approved for use.

**What measures are being taken to ensure the safe and effective use of Sodium Cromoglicate?**
A Risk Management Plan has been developed to ensure that Sodium Cromoglicate 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 Sodium Cromoglicate 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 Sodium Cromoglicate
A Marketing Authorisation was granted in the UK on 08 December 2017.

The full PAR for Sodium Cromoglicate follows this summary.

For more information about treatment with Sodium Cromoglicate read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2018.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 10</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and</td>
<td>Page 10</td>
</tr>
<tr>
<td></td>
<td>recommendation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Table of content of the PAR update</td>
<td>Page 12</td>
</tr>
</tbody>
</table>


I  INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aspire Pharma Limited a Marketing Authorisation for the medicinal product Sodium Cromoglicate 2% w/v Eye Drops, Solution (eye drops) (PL 35533/0084) on 08 December 2017. The product is a pharmacy medicine (P), indicated for the relief and treatment of seasonal and perennial allergic conjunctivitis.

This application was submitted as abridged national application, according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The applicant has cross-referred to Opticrom Allergy 2.0% w/v Eye Drops, Solution originally granted to Fisons Limited on 17 December 1985 (PL 00113/0039) and subsequently underwent several changes of ownership procedures with the current marketing authorisation holder being Aventis Pharma Limited on 28 February 2003 (PL 04425/0323).

Sodium cromoglicate exerts its effect locally in the eye. In vitro and in vivo animal studies have shown that sodium cromoglicate inhibits the degranulation of sensitised mast cells which occurs after exposure to specific antigens. Sodium cromoglicate acts by inhibiting the release of histamine and various membrane derived mediators from the mast cell. Sodium cromoglicate has demonstrated the activity in vitro to inhibit the degranulation of non-sensitised rat mast cells by phospholipase A and subsequent release of chemical mediators. Sodium cromoglicate did not inhibit the enzymatic activity of released phospholipase A on its specific substrate. Sodium cromoglicate has no intrinsic vasoconstrictor or antihistamine activity.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being a hybrid medicinal product of the reference product that has been licenced for over 10 years.

Comparable physicochemical parameters between the reference and proposed products were provided. As the product is a solution, no therapeutic equivalence study between the reference product Opticrom Allergy 2.0% w/v Eye Drops, Solution (PL 04425/0323) and the proposed product has been conducted.

The MHRA 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 MHRA 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 Marketing Authorisation was granted in the UK on 08 December 2017.
II QUALITY ASPECTS

II.1 Introduction
The finished product is formulated as an eye drop solution containing 2.0% w/v of the active ingredient sodium cromoglicate. The excipients present are disodium edetate, benzalkonium chloride and water for injections.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used in this product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in low density polyethylene (LDPE) bottles with a low density polyethylene (LDPE) under-cap and a high density polyethylene (HDPE) tamper proof cap containing either 5ml or 10ml of the solution. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Disodium 5,51-[2-hydroxypropane-1,3-diyl]bis(oxy)] bis[4-oxo-4H-1-benzopyran-2-carboxylate.
4H-1-Benzopyran-2-carboxylic acid, 5,51-[(2-hydroxy-1,3-propanediyl)bis(oxy)], bis[4-oxo-disodium salt]
Disodium 5,51-[2-hydroxytrimethylene dioxy]bis[4-oxo-4H-1-benzopyran-2-carboxylate.

Structure:

Molecular formula: C_{23}H_{14}Na_{2}O_{11}
Molecular weight: 512.34 g/mol
Appearance: White or almost white, crystalline, odourless powder, hygroscopic
Solubility: Freely soluble in water, practically insoluble in alcohol (96% ethanol), in Chloroform and in Ether

Sodium cromoglicate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, sodium cromoglicate, 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 of the development programme was to develop a stable eye drop solution that could be considered as a hybrid medicinal product of the currently licensed product, Opticrom Allergy 2.0% w/v Eye Drops, Solution (Aventis Pharma Limited).

The physicochemical properties of the proposed product versus the reference product have shown that the products are comparable.

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 commercial 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.

The data from these studies support a shelf-life of 30 months for unopened bottles with no special storage conditions. The in-use shelf life of the product is 4 weeks after first opening the bottle.

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

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

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium cromoglicate 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)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment Since Sodium Cromoglicate 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
There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of Sodium Cromoglicate are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In accordance with the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) “A waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved”, therefore no bioequivalence study was conducted or required.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

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 Sodium Cromoglicate.

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

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hypersensitivity to sodium cromoglicate or to any of the excipients</td>
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<td>• Eye irritation caused by Benzalkonium chloride</td>
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<td>• Discoloration of soft contact lenses occurred by contact with product</td>
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<td></td>
<td>• Use four weeks after opening of the bottle</td>
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<td></td>
<td>• Transient blurring of vision</td>
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<tr>
<td>Important potential risks</td>
<td>None</td>
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<tr>
<td>Missing information</td>
<td>• No data available on sodium cromoglicate excretion in human breast milk</td>
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<td>• Lack of interaction studies</td>
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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of 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 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.

IV 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 sodium cromoglicate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for this medicine is presented below:
Annex 1

Table of content of the PAR update

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

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