Public Assessment Report

Decentralised Procedure

Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution

(sodium cromoglicate)

Procedure No: UK/H/5451/001/DC

UK Licence No: PL 04425/0688

Aventis Pharma Limited (T/A Sanofi-aventis or Sanofi)
LAY SUMMARY
Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution
(Sodium cromoglicate)

This is a summary of the Public Assessment Report (PAR) for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution (PL 04425/0688). It explains how Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution.

For practical information about using Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution and what is it used for?
Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution is a ‘hybrid generic medicine’. This means that it is similar to a reference medicine (Opticrom™ Allergy 2.0% w/v Eye Drops, Solution) containing the same active substance, but different by its excipient composition and change of container type from multiple containers to a single container.

The company has provided additional own data to demonstrate the safety and efficacy of Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution regarding these differences from the reference medicine.

Opticrom Allergy Single Dose is used to relieve and treat eye allergies in adults and children.

There are two types of eye allergy:
  • ‘perennial allergic conjunctivitis’ – this can happen at any time of the year
  • ‘hay fever’ or ‘seasonal allergic conjunctivitis’ – this happens in different seasons and is caused by different pollens. Signs of allergies include itchy, watery, red or inflamed and puffy eyes.

How does Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution work?
Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution contains a substance called sodium cromoglicate which belongs to a group of medicines known for their anti-allergy activity. It works by stopping the release of the natural substances in the eyes that can lead to an allergic reaction.

How is Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution used?
Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution is for use as eye drops. The dosage for adults and children is usually 1-2 drops administered into each eye four times daily. There is no evidence to suggest that a different dose is needed for elderly patients.

As with most ophthalmic preparations, contact lenses should be removed before using Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution and may be inserted after 15 minutes.

Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution can be obtained from a pharmacy.

For further information on how Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution have been shown in studies?
Because Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution is a hybrid application and is considered to be therapeutically equivalent, to the reference product, Opticrom™ Allergy 2.0% w/v Eye Drops, Solution, their benefits and risks are taken as being the same as those of Opticrom™ Allergy 2.0% w/v Eye Drops, Solution.

**What are the possible side effects from Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution, see section 4 of the package leaflet.

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

**Why is Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution approved?**
It was considered that the benefits of using Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution to relieve and treat eye allergies 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 Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution?**
A risk management plan has been developed to ensure that Opticrom Allergy Single Dose 2% w/v 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 Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution**
Belgium, Croatia, Czech Republic, Italy, Luxemburg, Poland, Republic of Ireland, Slovak Republic, Spain and the UK agreed to grant a Marketing Authorisation for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution on 7th November 2014. A Marketing Authorisation was granted in the UK on 22nd December 2014.

For more information about using Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution follows this summary.

This summary was last updated in February 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution (PL 04425/0688; UK/H/5451/001/DC) indicated for the relief and treatment of seasonal and perennial allergic conjunctivitis, is approvable.

This Decentralised application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The applicant has cross-referred to Opticrom\textsuperscript{TM} Allergy 2.0% w/v Eye Drops, Solution. This product was originally licensed to CP Pharmaceuticals Limited as Visicrom Eye Drops 2% w/v (PL 04543/0169) on 1\textsuperscript{st} October 1992. The product underwent a change of ownership application on 2\textsuperscript{nd} October 1992 to Fisons Limited (PL 00113/0161) and a further change of ownership procedure to the current Marketing Authorisation holder Aventis Pharma Limited (PL 04425/0323) on 28\textsuperscript{th} February 2003.

This hybrid application seeks to introduce a new formulation (single dose as opposed to multi-dose container) and includes sodium chloride as an excipient instead of benzalkonium chloride and disodium edetate.

With UK as the RMS in this Decentralised Procedure (UK/H/5451/001/DC), Aventis Pharma Limited (T/A Sanofi-aventis or Sanofi) applied for the Marketing Authorisation for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution in Belgium, Croatia, Czech Republic, Italy, Luxemburg, Poland, Republic of Ireland, Slovak Republic and Spain.

\textit{In vitro} and \textit{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.

As per the Appendix II of the EMA Guideline on the investigation of bioequivalence and the Note for Guidance on the clinical requirements for locally applied locally acting products containing known constituents, in order to demonstrate that the differences in the excipients do not have an influence on the therapeutic equivalence between the to-be-registered product and the reference product, an appropriate \textit{in-vitro} study comparing relevant pharmaceutical properties of both products was performed.

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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 208 – 7\textsuperscript{th} November 2014). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 04425/0688) for this product on 22\textsuperscript{nd} December 2014.
II QUALITY ASPECTS

II.1 Introduction
This product is an eye drop solution and contains 2% w/v sodium cromoglicate, as active ingredient. The excipients present are sodium chloride and purified water.

All excipients used comply with their respective European Pharmacopoeia monographs.

The finished product is packaged in a low density polyethylene (LDPE) single dose container containing 0.3 ml solution; 10 or 20 of these containers are packed in an aluminium sachet. 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: Sodium cromoglicate
Chemical name(s): Disodium 5,5’-[2-hydroxypropane-1,3-diy]bis((oxy)bis(4-oxo-4H-1-benzopyran-2-carboxylate)

Structure:

Sodium cromoglicate is practically soluble in water and practically insoluble in ethanol.

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 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 in a single dose container with the absence of a preservative.

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.
**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 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 3 years for unopened sachets with storage conditions ‘Store below 25°C’ and ‘Keep the single dose containers in the aluminium sachet in order to protect from light’, and a shelf-life of 28 days after opening the sachet have been set. After opening the single-dose container, the medicinal product must be used immediately. Any remaining contents should be discarded after use.

The proposed shelf-lives and storage conditions 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**
As sodium cromoglicate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. An overview based on a literature review is appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

**III.2 Pharmacology**
No new data have been submitted and none are required for applications of this type.

**III.3 Pharmacokinetics**
No new data have been submitted and none are required for applications of this type.

**III.4 Toxicology**
No new data have been submitted and none are required for applications of this type.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
A suitable justification has been provided for not submitting an environmental risk assessment.

**III.6 Discussion on 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**
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of sodium cromoglicate are well known. The applicant’s clinical overview has been written by an appropriately qualified person
and is considered acceptable.

The proposed product differs from the reference product by its excipient composition and the container type (a single container rather than a multiple-use container).

In support of this application, the Marketing Authorisation Holder has conducted an in vitro study in order to demonstrate that the differences in the excipients do not have an influence on the therapeutic equivalence between the proposed product and the reference product.

IV.2 Pharmacokinetics

Sodium cromoglicate is poorly absorbed. When multiple doses of sodium cromoglicate ocular solution are instilled into normal rabbit eyes, less than 0.07% of the administered dose of sodium cromoglicate is absorbed into the systemic circulation (presumably by way of the eye, nasal passages, buccal cavity and gastrointestinal tract).

Trace amounts (less than 0.01%) of the sodium cromoglicate does penetrate into the aqueous humour and clearance from this chamber is virtually complete within 24 hours after treatment is stopped.

In normal volunteers, analysis of drug excretion indicates that approximately 0.03% of sodium cromoglicate is absorbed following administration to the eye.

The applicant has requested a biowaiver. To demonstrate that the differences in excipient composition between the proposed product and the reference product do not have any influence on the therapeutic equivalence, an in-vitro study was conducted to compare the pharmaceutical properties of the proposed product and reference product. This comparative study was performed on 3 batches of the proposed product, manufactured by the Company partner Unither, versus 3 batches of the reference product, manufactured by the Applicant’s manufacturing site (Sanofi Winthrop Industrie – Le Trait), 1 batch per fill volume (5 mL, 10 mL, and 13.5 mL).

The applicant has also included three studies to show that excluding the excipient, benzalkonium chloride, will have no effect on efficacy or safety of the product.

The studies show that both subjective and objective measures of efficacy between preservative-free and benzalkonium chloride-containing formulations are similar, with no statistical or clinically meaningful differences in efficacy seen across the three studies.

The biowaiver is accepted. Sodium cromoglicate acts on the conjunctival mast cells and as such the benzalkonium chloride’s ability to increase the penetration of actives through the cornea (a more deeply lying structure) should not alter the efficacy profile of the preservative free formulation versus the one containing benzalkonium chloride. All the three studies show similar efficacy for preservative containing and preservative-free formulations. In general, the removal of benzalkonium chloride from the formulation can be seen as a positive step as it should improve the tolerance profile of the medicine.

IV.3 Pharmacodynamics

Sodium cromoglicate has a variety of activities, which include inhibiting activation of many cell types including mast cells (stabilization of mast-cell membranes) which occurs after exposure to specific allergens and therefore inhibiting release of inflammatory mediators including cytokines from mast cells. Sodium cromoglicate also acts by reversing increased functional activation in leukocytes, suppressing the activating effects of chemotactic peptides on human neutrophils, eosinophils, and monocytes, and inhibiting parasympathetic reflexes. It has no intrinsic antihistaminic action and has generally been considered to possess no bronchodilator activity.
Sodium cromoglicate 2% w/v eye drops solution, which is applied locally, is intended to exert its inhibition of mast cell degranulation/mast cell stabilization effect at the site of application independently of its absorption into the systemic circulation.

A local tolerance study has also been included. The test product used in the study, sodium cromoglicate CRID 2% w/v eye drops solution single dose (SD), has the same qualitative and quantitative composition as the proposed product, Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution, in active substance and excipients. The reference multiple dose (MD) product used in the study, Optirol® eye drops solution MD, currently registered in France, had the same qualitative and quantitative composition in active pharmaceutical ingredient (API) and excipients as the Applicant’s reference product (Opticrom Allergy 2% w/v eye drops solution MD).

Methods:
This was a Phase 3, single-centre, randomised, parallel-group, open study comparing the ocular tolerability of sodium cromoglicate CRID 2% w/v eye drops solution SD versus Optirol 2% w/v eye drops solution MD. A total of 60 patients (30 per gender) aged 18 years and over and who had eye symptoms potentially caused by allergy or irritation were randomised to one of the treatment groups. Patients were to receive 1 to 2 drops of treatment in each eye, 4 to 6 times daily, for 6 to 10 days. Subjective symptoms including pricking, burning, photophobia, and watery discharge, as well as objective symptoms including conjunctival hyperemia and edema were scored. A score was attributed, for each eye, to all the symptoms, and the sum of scores for the right eye and the left eye made it possible to calculate the sum of subjective symptoms from 0 to 24 and the sum of objective symptoms from 0 to 12, for each patient. Subjective and objective symptoms were assessed before instillation, immediately after instillation, and 30 minutes after instillation on both at Day 0 and at the end of treatment (Dend), which occurred between Day 6 and Day 10.

Results:
Treatment groups were well balanced in terms of patients’ ages and characteristics at baseline including objective and subjective ocular symptom intensity scores. In addition, there were no differences in treatment duration and number of instillations (4.0 ± 0.0) prescribed between treatment groups. Four patients (2 in each treatment group) were excluded from the analysis due to missing data. At Dend, subjective symptom scores were reduced by approximately 6 to 7.5 points and objective symptom scores by approximately 3.5 points. Comparison of the means using the Mann-Whitney test showed that there was no difference in the reduction in symptom scores between the preservative-free SD product and the preservative-containing product MD, except for the subjective symptoms reported immediately after the application in favour of the preservative-free product SD (p=0.05). Ten patients receiving the reference MD product Optirol and 3 patients receiving the SD test product sodium cromoglicate CRID reported symptoms including stinging, pricking, and burning sensations that they experienced on instillation during the study. The intensity of these sensations on instillation was always described as mild, with the exception of 1 patient in the Optirol group who withdrew from the study due to intolerance to treatment. No serious adverse events (SAEs) were reported during the study.

The pharmacodynamics of sodium cromoglicate is well described. The studies presented are acceptable. The local tolerance study shows that the test and reference products had similar tolerability profiles with no significant safety concerns.

IV.4 Clinical efficacy
A suitable summary of the efficacy of sodium cromoglicate has been provided. As this is a hybrid application, the applicant is basing the efficacy profile on the reference product. The applicant has also included a bibliographic summary of the available data on sodium cromoglicate. The studies can be broken down into three main groups, placebo controlled studies, active controlled studies and a meta-analysis.
The placebo controlled studies clearly showed that in allergic rhinitis sodium cromoglicate is significantly better than placebo at subjectively and objectively treating the condition. This is also judged to be the case from patient and physician based end points. This holds true for both seasonal and perennial allergic rhinitis.

The studies comparing topical mast cell stabilisers show that there are no significant clinical differences between the different actives when it comes to allergic rhinitis and that when a placebo arm was included, that sodium cromoglicate was better than placebo.

When compared to topical antihistamines, some studies showed that there were no significant clinical differences between actives. Others showed that topical antihistamines were more effective than sodium cromoglicate. A couple of these further showed that sodium cromoglicate could not be separated from placebo. However, most were in favour of the efficacy of sodium cromoglicate.

When compared to dual acting topical antihistamine/mast cell stabilisers it was generally found that both actives were efficacious, with both being better than placebo. One study showed that the dual acting active had similar efficacy to sodium cromoglicate, whilst the other showed that cromoglicate was effective but that the dual acting active was better.

Finally the meta-analysis showed that patients using sodium cromoglicate were 17 times more likely to perceive benefit than those using placebo.

Overall, the efficacy of sodium cromoglicate is established.

IV.5 Clinical safety
As this is a hybrid application the safety profile is taken from the reference product. The applicant has provided the post marketing data for the reference product, bibliographic data and a local tolerance study which is discussed in the pharmacodynamics section (IV.3).

The post marketing and bibliographic data showed that sodium cromoglicate is a well-tolerated product with much worldwide use. The adverse events seen are mostly due to its topical nature and affect the eyes. Few serious adverse events (SAEs) are recorded and most are not attributable to this active. It is therefore accepted that the safety profile of sodium cromoglicate is well-established.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) 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 Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution.
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<th>Additional risk minimisation activities</th>
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<td>Important potential risks</td>
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<td>Use during pregnancy and lactation</td>
<td>Effect on fertility</td>
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Summary table of risk minimisation measures

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<td>- Use during pregnancy and lactation</td>
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<td>As with all medication, caution should be exercised especially during the first trimester of pregnancy. Cumulative experience with sodium cromoglicate suggests that it has no adverse effects on foetal development. It should be used in pregnancy only where there is a clear need. Breast-feeding</td>
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IV.7  Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V  User consultation
The package leaflet has been evaluated for Opticrom Allergy Single Dose 2% w/v Eye Drops, Solution 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.

IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Sodium cromoglicate is a well-known and widely used active substance with an established efficacy and safety profile. The changes in the formulation have been justified and the studies presented show that the removal of benzalkonium chloride should not affect efficacy or safety of the product. Extensive clinical experience with sodium cromoglicate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment 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.

Labelling
Opticrom® Allergy Single Dose 2% w/v Eye Drops Solution
Sodium cromoglicate

Each single dose container contains 2% w/v of sodium cromoglicate.
Other Ingredients: sodium chloride, purified water.
Preservative free.
10 single dose containers.
Each single dose container contains 0.3 ml of solution.
Read the package leaflet before use.
Do not swallow. Ocular use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
After opening the sachet: 28 days.
After opening single dose container: must be used immediately.

Before opening single dose container: store below 25°C.
Keep the single dose containers in the aluminium sachet in order to protect from light.
After opening single dose container: throw away any remaining contents after use.
INSTRUCTIONS FOR USE:
Opticrom® Allergy Single Dose is used for the relief and treatment of eye allergies in adults and children.
Contact lenses should be removed before each application and can be inserted after 15 minutes.
Recommended dose: 1 or 2 drops in each eye 4 times a day. Do not use this medicine if you are allergic to sodium cromoglicate, or to any other ingredients of this medicine. If you are not sure, talk to a doctor or pharmacist before using Opticrom® Allergy Single Dose.
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