Cromo Singles 2% w/v Eye Drops  
(sodium cromoglicate)  

PL 17248/0003  

UKPAR  

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Cromo Singles 2% w/v Eye Drops
(sodium cromoglicate)

PL 17248/0003

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Four Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Cromo Singles 2% w/v Eye Drops (PL 17248/0003) on 24 May 2013. This medicine is a pharmacy (P) medicine, available only from pharmacies under the supervision of a pharmacist. Cromo Singles 2% w/v Eye Drops prevent and relieve allergic conjunctivitis (eye irritation) in conditions such as hay fever, chronic allergic conjunctivitis and vernal kerato conjunctivitis. The product contains sodium cromoglicate 2% for single use.

Cromo Singles 2% w/v Eye Drops contain the active ingredient sodium cromoglicate, which works by inhibiting the agents which cause the allergic reaction.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Cromo Singles 2% w/v Eye Drops outweigh the risks and a Marketing Authorisation were granted.
Cromo Singles 2% w/v Eye Drops
(sodium cromoglicate)

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Four Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Cromo Singles 2% w/v Eye Drops (PL 17248/0003) on 24 May 2013. The product is a pharmacy (P) medicine available from pharmacies and is indicated for prophylaxis and symptomatic relief in acute allergic conjunctivitis such as hay fever, chronic allergic conjunctivitis and vernal kerato conjunctivitis.

This application was submitted under Article 10(1) of Directive 2001/83/EC (as amended), claiming to be a generic medicinal product of Opticrom Aqueous Eye Drops (PL 00113/0039R; Fisons plc, UK) first licensed in the UK in 17 December 1985. The reference product Opticrom Aqueous Eye Drops (PL 00113/0039R; Fisons plc, UK) is presented in a multi-dose bottle whilst Cromo Singles 2% w/v Eye Drops is presented in single dose units. Cromo Singles 2% w/v Eye Drops does not contain the benzalkonium chloride or disodium edetate that are present in Opticrom Aqueous Eye Drops (Fisons plc, UK).

The active ingredient, sodium cromoglicate inhibits the degranulation of sensitised mast cells which normally occurs after exposure to specific allergens and thereby prevents the release of allergic mediators such as histamine. It is poorly absorbed from the eye (approximately 0.03% in healthy volunteers) due to its lipid insolubility.

No new non-clinical or clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years. No bioequivalence studies have been performed and none are required for this application, since Cromo Singles 2% w/v Eye Drops is an ophthalmic solution intended for local use (that is, not systemic) and contains the same concentration of the same active substance as the reference product (CPMP/EWP/239/95). Bioequivalence to the originator product is based on the comparative quality attributes of the product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of using Cromo Singles 2% w/v Eye Drops outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Sodium cromoglicate
Chemical name: Disodium 4,4'-dioxo-5,5'-[(2-hydroxytrimethylenedioxy)di(chromene-2-carboxylate);
   (4H-1-Benzopyran-2-carboxylic acid, 5,5'-%[2-hydroxy-1,3-propanediyl]bis(oxy)]bis[4-oxo-, disodium salt;
Disodium 5,5'-%[2-hydroxy-1,3-propanediyl]dioxy]bis(4-oxo-4H-chromene-2-carboxylate);
Disodium 5,5'-%[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
Appearance: White or almost white, crystalline powder, hygroscopic, soluble in water, practically insoluble in alcohol and 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 European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

DRUG PRODUCT

Other Ingredients
Purified water is the only pharmaceutical excipient. Appropriate justification for the inclusion of purified water has been provided.

Purified water complies with its European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided for, showing compliance with the proposed specification.

Purified water does not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programmes was to formulate a safe efficacious, stable single-dose, single-use product comparable in performance to the reference product Opticrom Aqueous Eye Drops (Fisons plc, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative physicochemical data and impurity profiles have been provided for this product and the reference product.
Manufacturing Process
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 with full production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
Cromo Singles 2% w/v Eye Drops are packaged in low density polyethylene (LDPE) single-dose containers fitted with twist and pull off tamper-evident seals containing 0.4ml eye drops. The product is supplied as 20 single dose containers (4 strips of 5 single-dose containers) in an outer carton.

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.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened product, with the storage conditions ‘Do not store above 25°C. Keep the single dose containers in the outer carton for protection from light.’

The product should be administered immediately after first opening the single-dose container opening. Any unused solution should be discarded immediately after initial administration.

Bioequivalence
No bioequivalence studies are presented for this aqueous medicinal product. This is acceptable since this product is a solution intended for local use (that is, not systemic) and contains the same concentration of the same active substance as the reference product (CPMP/EWP/239/95).

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA (Marketing Authorisation Application) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium cromoglicate are well-known, no new non-clinical data have been submitted and none are required.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of sodium cromoglicate is well-known.

No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for an aqueous topical product. Bioequivalence to the reference product is based on the comparative quality attributes of the product. No bioequivalence study has been conducted as this product, being an eye drop, is administered via a topical route and has no systemic activity. The justification for a biowaiver is acceptable.

Efficacy
The efficacy of sodium cromoglicate is well-known. No new efficacy data have been submitted and none are required for this application.

Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application. As an active ingredient, sodium cromoglicate has a well-established safety profile and an acceptable level of safety in the proposed indications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the MAH, fulfills the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this application.

Conclusion
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Cromo Singles 2% w/v Eye Drops are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of sodium cromoglicate are well-known, no additional data were required.

EFFICACY
No clinical studies have been conducted to support the application. Bioequivalence to the originator product is based on the comparative quality attributes of the product. No bioequivalence study has been conducted as this product, being an eye drop, is administered via a topical route and has no systemic activity. The justification for a biowaiver is acceptable.

SAFETY
The safety profile of sodium cromoglicate is well-known. No new safety data were submitted and none were required for this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
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 compounds. The benefit/risk balance is, therefore, considered to be positive.
**Cromo Singles 2% w/v Eye Drops**
**(sodium cromoglicate)**

**PL 17248/0003**

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**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the Marketing Authorisation application on 08 November 2001.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 07 May 2008.


5. The application was granted on 24 May 2013.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
UKPAR Cromo Singles 2% w/v Eye Drops

LABELLING

Carton labelling:

Each 0.4ml single-dose container contains: Sodium Cromoglicate 2% w/v as the active ingredient. Also contains Purified Water.

MA Holder: Four Pharmaceuticals Ltd, 23 Upper Green Road, Tewin, Welwyn, Hertfordshire, AL6 0LE

PL 17249/0003

White Carton

Printing
Red PMS 032
Green PMS 355
Black

20 single-dose containers of 0.4ml

Cromo Singles 2% w/v Eye Drops
sodium cromoglicate

For ocular use only.

Dose: One or two drops to be administered into each affected eye 4 times a day.

The eye drops are supplied in single-dose containers for single-dose use only. The eye drops should only be used if the solution is clear, not discoloured, free from particles and the container is intact and undamaged. The sterile eye drops should be administered immediately after opening the sealed container. Any unused solution should be discarded immediately after initial use.

Please read the enclosed package leaflet before use and follow the instructions.

Soft contact lenses should not be worn whilst using this product
Do not store above 25°C
Keep the single-dose containers in the outer carton to protect from light.
Keep out of the reach and sight of children

Box indicates position of Braille text
20 single-dose containers of 0.4ml

Cromo Singles 2% w/v Eye Drops
sodium cromoglicate

Attach dispensing label here

Barcode position
Visual only

Ref no: 4P003-C1
Braille text to be added as indicated in blue box

cromo singles
2% w/v
eye drops

Labelling for single dose immediate packaging:

Cromo Singles 2% w/v
Eye Drops 0.4ml
sodium cromoglicate

Lot number as Lot: XXXXX and expiry date as Exp: MM YYYY are embossed on the plastic of the tag for each single dose unit