Public Assessment Report

Decentralised Procedure

Olopatadine Zentiva 1 mg/ml eye drops, solution

(olopatadine hydrochloride)

Procedure No: UK/H/4964/001/DC

UK Licence No: PL 17780/0568

Winthrop Pharmaceuticals UK Limited
LAY SUMMARY

On 02 September 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Winthrop Pharmaceuticals UK Limited, trading as Zentiva, a Marketing Authorisation for the medicinal product Olopatadine Zentiva 1 mg/ml eye drops, solution (PL 17780/0568; UK/H/4964/001/DC). This is a prescription-only medicine (POM) used for the treatment of signs and symptoms of seasonal allergic conjunctivitis.

**Allergic conjunctivitis:** Some materials (allergens) like pollens, house dust or animal fur may cause allergic reactions resulting in itching, redness, as well as swelling of the surface of the eye.

The active ingredient, olopatadine (as olopatadine hydrochloride), is a medicine for treatment of allergic conditions of the eye. It works by reducing the intensity of the allergic reaction.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Olopatadine Zentiva 1 mg/ml eye drops, solution outweigh the risks and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Olopatadine Zentiva 1 mg/ml eye drops, solution</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid, Article 10(3)</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Olopatadine hydrochloride</td>
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<td><strong>Form</strong></td>
<td>Eye drops, solution</td>
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<tr>
<td><strong>Strength</strong></td>
<td>1 mg/ml olopatadine (as olopatadine hydrochloride)</td>
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<td><strong>MA Holder</strong></td>
<td>Winthrop Pharmaceuticals UK Limited</td>
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<td><strong>Reference Member State (RMS)</strong></td>
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<td><strong>Concerned Member States (CMS)</strong></td>
<td>Bulgaria, Cyprus, Czech Republic, Poland and Romania</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/4964/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 196 – 01 August 2013</td>
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Module 2

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.
Module 3
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.
# Module 4

## Labelling

The Marketing Authorisation Holder has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

## Minimum particulars to appear on small immediate packaging units

### 1. Name of the medicinal product and route(s) of administration

Olopatadine 1 mg/ml eye drops
Olopatadine

### 2. Method of administration

Ocular use

### 3. Expiry date

EXP
Discard four weeks after first opening.

### 4. Batch number

Lot

### 5. Contents by weight, by volume or by unit

5 ml

### 6. Other
Olopatadine Zentiva 1 mg/ml eye drops, solution.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper box

1. **NAME OF THE MEDICINAL PRODUCT**

Olopatadine 1 mg/ml eye drops, solution
Olopatadine

2. **STATEMENT OF ACTIVE SUBSTANCE**

1 ml of solution contains 1 mg olopatadine (as hydrochloride).

3. **LIST OF EXCIPIENTS**

Excipients: benzalkonium chloride; hydrochloric acid; disodium phosphate dodecahydrate; sodium chloride; water for injection

4. **PHARMACEUTICAL FORM AND CONTENTS**

Eye drops, solution
1 x 5 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Ocular use.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
Discard four weeks after first opening.
9. **SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Trading as Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 17780/0568

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Olopatadine 1 mg/ml eye drops, solution
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Olopatadine Zentiva 1 mg/ml eye drops, solution (PL 17780/0568; UK/H/4964/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for treatment of ocular signs and symptoms of seasonal allergic conjunctivitis.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Bulgaria, Cyprus, Czech Republic, Poland and Romania as Concerned Member States (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as a hybrid application. The reference medicinal product for this application is Opatanol 1mg/ml eye drops, solution (Alcon Laboratories [UK] Limited) which was first authorised in the EEA via the Centralised procedure (EU/1/02/217/001-002) on 17 May 2002.

The active ingredient, olopatadine hydrochloride, is a selective H1-receptor antagonist, inhibiting the release of histamine, and other proinflammatory mediators, from mast cells.

No new non-clinical or clinical data have been submitted, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years. No therapeutic studies have been performed and none are required for this application for an aqueous ophthalmic solution, conforming to Guideline CPWP/EWP/QWP/1401/98 Rev.1 Corr**).

Olopatadine Zentiva 1 mg/ml eye drops, solution was developed to be identical to the reference product Opatanol 1mg/ml eye drops, solution with respect to the concentration of the active substance, and its physiochemical properties (see Clinical Aspects, Section III.3).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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 manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 196) on 01 August 2013. After a subsequent national phase, a licence was granted in the UK on 02 September 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Olopatadine Zentiva 1 mg/ml eye drops, solution</th>
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<tbody>
<tr>
<td>Name of the active substance (INN)</td>
<td>Olopatadine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Ophthalmologicals; decongestant and antiallergics; other antiallergics (ATC code: S01GX 09)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Eye drops, solution; 1 mg/ml olopatadine (as olopatadine hydrochloride)</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/4964/001/DC</td>
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<td>United Kingdom</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Winthrop Pharmaceuticals UK Limited</td>
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III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Olopatadine hydrochloride
Chemical name: Dibenz[b,e]oxepin-2-acetic acid, 11-[3-(dimethylamino)propylidene]-6, II-dihydro-,hydrochloride, (Z)

Structural formula:

![Structural formula of Olopatadine hydrochloride](image)

Molecular formula: \((\text{C}_{21}\text{H}_{23}\text{NO}_3)\cdot\text{HCl}\)
Molecular Weight: 373.87
Appearance: An off-white to white crystalline powder.
Solubility Very soluble in formic acid, sparingly soluble in water and very slightly soluble in dehydrated alcohol.

Olopatadine hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately 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 foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients benzalkonium chloride, hydrochloric acid (E507; for pH adjustment), disodium phosphate dodecahydrate (E339), sodium chloride and Water for injections. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis are provided for each excipient showing compliance with their respective monographs.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a robust stable ophthalmic preparation containing 5.0 mg of olopatadine (as olopatadine hydrochloride) in 5 ml of solution that was pharmacologically equivalent and comparable in performance to the reference product, Opatanol 1 mg/ml eye drops (Alcon Laboratories [UK] Ltd).

Suitable pharmaceutical development data have been provided for this application.

Comparative physico-chemical parameter data and impurity profiles have been provided for this product and the originator product, Opatanol 1 mg/ml eye drops (Alcon Laboratories [UK] Ltd).

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated using production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specification proposed for the product is acceptable. Test methods have been described and have been 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**

The finished product is supplied in 5 ml opaque low-density polyethylene (LDPE) bottles with LDPE droppers and high-density polyethylene (HDPE) tamper-proof screw-caps. The product is packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons, in a pack size of 1 × 5 ml bottle.

Satisfactory specifications and Certificates of Analysis for all packaging material have been provided. All primary packaging complies with current European regulations concerning plastic immediate packaging materials.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the product stored in the unopened container has been set. The product should be discarded
four weeks after first opening. The storage instructions for the product are “Store in the original package in order to protect from light.”

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

**Bioequivalence/Bioavailability**
As the product provides local therapeutic activity (that is, not systemic), investigation of bioequivalence is not appropriate for this product. Sufficient evidence has been provided to demonstrate that the physicochemical properties of Olopatadine Zentiva 1 mg/ml eye drops, solution and of the reference product, Opatanol 1 mg/ml eye drops (Alcon Laboratories [UK] Limited) are equivalent. As satisfactory evidence of pharmaceutical equivalence to the innovator product has been provided, no further non-clinical or clinical studies were required or provided.

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

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant that makes reference to the user tested PILs for Opatanol 1 mg/ml eye drops, solution and Divare Soltab 5mg/10 mg.

**Marketing Authorisation Application (MAA) form**
The MAA form is satisfactory.

**Expert report (Quality Overall Summary)**
The quality overall summary has been 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.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of olopatadine hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview has been written by appropriately qualified persons and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for not submitting an Environmental Risk Assessment for this application.

The grant of a Marketing Authorisation is recommended.

**III.3 CLINICAL ASPECTS**
The clinical pharmacology of olopatadine hydrochloride is well-known.

No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is being made under Article 10.3 (hybrid) of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption - in this case – after ocular administration. In accordance with the “Guideline on the
Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) the applicant is not required to submit a therapeutic equivalence study.

Efficacy
The efficacy profile of olopatadine hydrochloride is well-known. Efficacy is reviewed in the clinical overview. No new efficacy data have been submitted and none are required for this application.

Safety
The safety profile of olopatadine hydrochloride is well-known. The safety profile of olopatadine hydrochloride is reviewed in the clinical overview. No new safety data have been submitted with this application and none are required.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the originator 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
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 applicant, fulfils the requirements and provides adequate evidence that the applicant 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 product.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV  OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Olopatadine Zentiva 1 mg/ml eye drops, solution 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 olopatadine hydrochloride are well-known, no additional data were required.

EFFICACY
No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is made under Article 10.3 (hybrid) of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption– in this case – after ocular administration. In accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) the applicant is not required to submit a therapeutic equivalence study.

The applicant’s product Olopatadine Zentiva 1 mg/ml eye drops, solution) has been demonstrated to be
pharmacologically equivalent to the reference product Opatanol 1 mg/ml eye drops (Alcon Laboratories [UK] Limited).

SAFETY
The safety profile of olopatadine hydrochloride 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 originator product, where appropriate, and consistent 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 olopatadine hydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL THE PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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