Public Assessment Report

Decentralised Procedure

Minims Povidone Iodine 5% w/v Eye Drops, Solution
(iodinated povidone)

Procedure No: UK/H/3952/001/DC

UK Licence No: PL 03468/0020

Bausch & Lomb (UK) Ltd
LAY SUMMARY

On 07 December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Bausch & Lomb UK Limited a Marketing Authorisation for the medicinal product Minims Povidone Iodine 5% w/v Eye Drops, Solution (PL 03468/0020; UK/H/3952/001/DC). This is a prescription-only medicine (POM).

Minims Povidone Iodine 5% w/v Eye Drops, Solution is a solution that contains an antiseptic known as iodinated povidone in an eye wash solution. Minims Povidone Iodine 5% w/v Eye Drops, Solution is used for cleaning the surface of the eye before eye surgery.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Minims Povidone Iodine 5% w/v Eye Drops, Solution, solution outweigh the risks and a Marketing Authorisation was granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure  
Module 2: Summary of Product Characteristics  
Module 3: Patient Information Leaflet  
Module 4: Labelling  
Module 5: Scientific Discussion  
  
  I Introduction  
  II About the product  
  III Scientific overview and discussion  
  III 1 Quality aspects  
  III 2 Non-clinical aspects  
  III 3 Clinical aspects  
  IV Overall conclusion and benefit/risk assessment  

Module 6: Steps taken after initial procedure
Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Minims Povidone Iodine 5% w/v Eye Drops, Solution</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Hybrid, Article 10.3</td>
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<td>Active Substance</td>
<td>Iodinated povidone</td>
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<td>Eye drops, solution</td>
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<td>MA Holder</td>
<td>Bausch &amp; Lomb UK Limited</td>
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<td>Kingston-Upon-Thames</td>
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<td>Reference Member State (RMS)</td>
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<td>UK/H/3952/001/DC</td>
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<td>Timetable</td>
<td>Day 210 – 03 October 2012</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
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 Minims Povidone Iodine 5% w/v Eye Drops, Solution (PL 03468/0020; UK/H/3952/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for cutaneous peri-ocular and conjunctival antisepsis prior to ocular surgery to support post-operative infection control.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Spain, Finland, France, Ireland, Luxembourg, The Netherlands, Norway, Portugal and Sweden 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 Betadine 5%, Solution for eye irrigation (Meda Pharma France, France) which was first authorised in France on 18 August 1992.

The active ingredient iodinated povidone belongs to the pharmacotherapeutic group ‘Ophthalmologicals; anti-infectives’.

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, conforming to Guideline CPWP/EWP/239/95. Minims Povidone Iodine 5% w/v Eye Drops, Solution is an ophthalmic solution and was developed to be identical to the reference product Betadine 5%, Solution for eye irrigation with respect to its qualitative and composition and 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 210) on 03 October 2012. After a subsequent national phase, a licence was granted in the UK on 07 December 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Minims Povidone Iodine 5% w/v Eye Drops, Solution |
| Name of the active substance (INN) | Iodinated povidone |
| Pharmacotherapeutic classification (ATC code) | Ophthalmologicals; anti-infectives; (ATC code: S01AX18) |
| Pharmaceutical form and strength | Eye drops, solution; 5% w/v |
| Reference number for the Decentralised Procedure | UK/H/3952/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Belgium, Spain, Finland, France, Ireland, Luxembourg, The Netherlands, Norway, Portugal and Sweden. |
| Marketing Authorisation Number | PL 03468/0020 |
| Name and address of the authorisation holder | Bausch & Lomb UK Limited 106 London Road Kingston-Upon-Thames Surrey KT2 6TN UK |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Iodinated Povidone
Chemical name: 2-pyrrolidinone-1-ethenyl-homopolymer complex with iodine.
Structural formula:

\[
\begin{align*}
\text{Molecular formula:} & \quad (C_6H_9NO)_n.xI \\
\text{Relative molecular mass:} & \quad \text{Variable} \\
\text{Appearance:} & \quad \text{Yellowish-brown or reddish-brown, amorphous powder} \\
\text{Solubility} & \quad \text{Soluble in water and in ethanol (96 %) and practically insoluble in acetone.}
\end{align*}
\]

Iodinated povidone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance Iodinated Povidone maleate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely glycerol, Nonoxinol 9, disodium phosphate anhydrous, citric acid monohydrate, sodium chloride, sodium hydroxide (for pH adjustment) and purified water. 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 that was pharmacologically equivalent and comparable in performance to the reference product, Betadine 5%, Solution for eye irrigation (Meda Pharma France, France).

Suitable pharmaceutical development data have been provided for this application.

Comparative physico-chemical parameter data have been provided for this product and the originator product, Betadine 5%, Solution for eye irrigation (Meda Pharma France, France).

**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 sealed polypropylene single-dose containers fitted with twist and pull off caps marked with “PVI 5.0”. Each single-dose container provides 0.5 ml of solution and is overwrapped in a polyethylene sachet. The product is packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 20 x 0.5 ml single dose containers.

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 18 months for the product stored in the unopened container has been set, with the storage conditions “Store between 2°C and 8°C. Store in the original package to protect from light.” The product may be stored without refrigeration at not more than 25°C for up to one month. After this period the product should be discarded.

Once opened, the product should be used immediately. Discard immediately after first use.

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 Minims Povidone Iodine 5% w/v Eye Drops, Solution are equivalent to the reference product, Betadine 5%, Solution for eye irrigation (Meda Pharma France, France).
Drops, Solution and of the reference product, Betadine 5%, Solution for eye irrigation (Meda Pharma France, France) 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 labelling are pharmaceutically acceptable.

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 PIL for Minim Phenylephrine Hydrochloride 2.5% and 10% Eye Drops, Solution.

**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 iodinated povidone 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.

An acceptable Environmental Risk Assessment has been submitted; no phase II assessment is required.

The grant of a Marketing Authorisation is recommended.

**III.3 CLINICAL ASPECTS**
The clinical pharmacology of iodinated povidone 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 iodinated povidone 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 iodinated povidone is well-known. The safety profile of iodinated povidone 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 guidelines. The labelling is in-line with the current guidelines.

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 Minims Povidone Iodine 5% w/v 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 iodinated povidone 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 Minims Povidone Iodine 5% w/v Eye Drops, Solution has been demonstrated to be pharmaceutically equivalent to the reference product Betadine 5%, Solution for eye irrigation (Meda Pharma France, France)

**SAFETY**
The safety profile of iodinated povidone 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 guidelines.

**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 iodinated povidone 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 PROCEDURE - SUMMARY

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<th>Outcome</th>
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