Public Assessment Report

Decentralised Procedure

KETOROLAC TROMETAMOL 0.5% W/V EYE DROPS, SOLUTION

Procedure No: UK/H/4540/001/DC

UK Licence No: PL 25298/0068

BROWN AND BURK UK LIMITED
LAY SUMMARY

On 18 February 2013, Germany and the UK agreed to grant a marketing authorisation to Brown and Burk UK Limited for the medicinal product Ketorolac trometamol 0.5% w/v eye drops, solution. This prescription-only medicine (POM) is used to prevent and relieve eye inflammation following surgery on the eye in adults.

The active ingredient is ketorolac trometamol. Ketorolac eye drops belong to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ketorolac trometamol 0.5% w/v eye drops, solution outweigh the risks, hence a Marketing Authorisation has been granted. National licences were granted in the UK on 19 March 2013.
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Module 1
Information about initial procedure

<table>
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<th>Product Name</th>
<th>Ketorolac trometamol 0.5% w/v eye drops, solution</th>
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<td>Type of Application</td>
<td>Hybrid application, Article 10(3)</td>
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<td>Active Substances</td>
<td>Ketorolac trometamol</td>
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<tr>
<td>Form</td>
<td>Eye drops solution</td>
</tr>
<tr>
<td>Strength</td>
<td>0.5% w/v</td>
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<tr>
<td>MA Holder</td>
<td>Brown &amp; Burk UK Ltd, 5, Marryat Close, Hounslow West, Middlesex, TW4 5DQ, UK</td>
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<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany</td>
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<tr>
<td>Procedure Number</td>
<td>UK/H/4540/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 18 February 2013</td>
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</table>
Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.

Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling

UKPAR Ketorolac Trometamol 0.5% w/v eye drops, solution

One ml solution contains 5mg ketorolac trometamol (0.5% w/v) sodium chloride, benzalkonium chloride, disodium edetate, octoxynol 40, sodium hydroxide and/or hydrochloric acid (to adjust pH), water for injection.

Ocular use.
Read the package leaflet before use.
Keep out of reach and sight of children.
This product known to discolor soft contact lenses. Remove contact lenses before use.
Discard any remaining solution 28 days after first opening.

PL 23298/0068
MA Holder: Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom
CODE: K/DRUGS/KTK/28357/2006

Affix Dispensing Label Here

32 mm

30 mm
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
On 18 February 2013, Germany and the UK agreed to grant a marketing authorisation to Burk and Brown UK Limited for the medicinal product Ketorolac trometamol 0.5% w/v eye drops, solution (PL 25298/0068; UK/H/4540/001/DC). This is a prescription-only medicine (POM) indicated for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery.

This application was submitted by the decentralised procedure as an abridged application according to Article 10.3 of Directive 2001/83/EC, a hybrid application, with Acular 0.5% w/v oogdruppels, oplossing (Allergan Pharmaceuticals Ireland Limited) as the reference product, which was initially granted a licence in the Netherlands on 07 December 1989. The reference product in the UK is Acular 0.5% w/v Eye drops, solution (Allergan Limited, UK).

Ketorolac trometamol is a member of the pyrrolo-pyrrole group of non-steroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. It is used to prevent and reduce post operative inflammation following ocular surgery. The advantage of topical therapy includes the ability to deliver a relatively high concentration of drug directly to the target tissue while avoiding potential problems associated with systemic administration.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a product that has been licensed for over 10 years. No therapeutic studies have been performed and none are required for this application, conforming to Guideline CPWP/EWP/239/95. Ketorolac trometamol 0.5% w/v eye drops, solution is an ophthalmic solution and was developed to be identical to the reference product Acular 0.5% w/v Eye drops, solution with respect to its qualitative composition and physiochemical properties (see Clinical Aspects).

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 and assembly of this product.

After a subsequent national phase, a licence was granted in the UK on 19 March 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ketorolac trometamol 0.5% w/v eye drops, solution</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ketorolac trometamol</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anti-inflammatory agents, non-steroids (S01BC05)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>0.5% w/v eye drops, solution</td>
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<td>UK/H/4540/001/DC</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Member States concerned</td>
<td>Germany</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 25298/0068</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Brown &amp; Burk UK Ltd, 5, Marryat Close, Hounslow West, Middlesex, TW4 5DQ, UK</td>
</tr>
</tbody>
</table>

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Ketorolac trometamol

INN: Ketorolac trometamol

Chemical name: (+)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid 1:1 salt with 2-amino-2-(hydroxymethyl)-1,3-propanediol

Structure:

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and enantiomer
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Molecular formula: C\textsubscript{15}H\textsubscript{13}NO\textsubscript{3}.C\textsubscript{4}H\textsubscript{11}NO\textsubscript{3}

Molecular weight: 255.27 + 121.14 = 376.41

Physical form: A white or almost white crystalline powder, freely soluble in water and methanol, slightly soluble in ethanol, practically insoluble in methylene chloride

Ketorolac trometamol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of ketorolac trometamol are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, benzalkonium chloride, disodium edetate, octoxynol 40, sodium hydroxide and/or hydrochloric acid (for pH adjustment), and water for injection.

With the exception of octoxynol 40 (which is controlled to a suitable in-house specification), all excipients used comply with their respective European Pharmacopoiea monograph. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with their respective monograph.

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

Pharmaceutical development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that is qualitatively identical to the originator product Acular 0.5% w/v Eye drops, solution (Allergan Limited, UK) and to achieve pharmaceutical equivalence in terms of physicochemical properties and dosage form performance.

A satisfactory account of the pharmaceutical development has been provided.

Comparative physico-chemical characteristics have been provided for the proposed product versus the originator product, and pharmaceutical equivalence has been shown.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on production-scale batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. 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

White low density polyethylene (LDPE) container, with translucent LDPE block nozzle and white high density polyethylene (HDPE) screw caps. Bottles are available as 3 ml, 5 ml and 10 ml eye drops. Each pack contains either 1 bottle of 3ml, 1 bottle of 5ml, 3 bottles of 5ml or 1 bottle of 10ml.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months (unopened) and 28 days (after opening) has been set with no specific storage conditions, which is satisfactory.

Bioequivalence/bioavailability

Essential similarity with the originator product is based on the comparative quality attributes of the product. The applicant refers to Notes for Guidance on the investigation of Bioavailability and Bioequivalence to justify the exemption from bioequivalence study. Additional in-vivo testing is not considered necessary, because not only the composition of the drug product is similar to the innovator
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

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 it contains.

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

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of ketorolac trometamol are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected. Therefore, no environmental risk assessment is required for this application.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Clinical Pharmacology and 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. The applicant refers to “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) to justify the exemption from bioequivalence study. Additional in-vivo testing is not considered necessary, because not only the composition of the drug product is similar to the innovator product, but also other characteristics, such as surface tension, viscosity, pH, osmolality and drop size are the same.

Safety
No new data have been submitted and none are required for an application of this type.

SmPC, PIL and Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

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.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Ketorolac trometamol 0.5% 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. Pharmaceutical equivalence with the originator product Acular 0.5% w/v Eye drops, solution (Allergan Limited, UK) has been shown through the qualitative composition of the products.

**NON-CLINICAL**
No new non-clinical data were submitted and none are required for an application of this type.

**CLINICAL**
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. The applicant refers to the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) to justify the exemption from bioequivalence study. Additional *in-vivo* testing is not considered necessary, because not only the composition of the drug product is similar to the originator product, but also other characteristics, such as surface tension, viscosity, pH, osmolality and drop size are the same.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

**BENEFIT-RISK ASSESSMENT**
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s product Ketorolac trometamol 0.5% w/v eye drops, solution and the reference product Acular 0.5% w/v Eye drops, solution (Allergan Limited, UK) are interchangeable. Extensive clinical experience with ketorolac trometamol is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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