Public Assessment Report

Scientific discussion

Brimonidine Warren 2 mg/ml, eye drops, solution

(brimonidine tartrate)

NL/H/3589/001/DC

Date: 7 August 2017

This module reflects the scientific discussion for the approval of Brimonidine Warren 2 mg/ml, eye drops, solution. The procedure was finalised on 8 December 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Brimonidine Warren 2 mg/ml, eye drops, solution from Warren Generics s.r.o.

The product is indicated for reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
- As monotherapy in patients in whom topical beta-blocker therapy is contraindicated.
- As adjunctive therapy to other intraocular pressure lowering medications when the target IOP is not achieved with a single agent (see SmPC section 5.1).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Alphagan 0.2% w/v (2 mg/ml) eye drops, solution (NL License RVG 21754) which has been registered in the Netherlands by Allergan Pharmaceuticals since 2 December 1997.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Brimonidine Warren 2 mg/ml is a clear, greenish-yellow solution, free from any visible particulate matter with pH 5.6-6.6 and osmolality 280-330 mOsm/kg.

One ml of solution contains as active substance 1.3 mg brimonidine, as 2.0 mg of brimonidine tartrate.

The solution is packed in gamma sterilised white LDPE bottles with a natural LDPE nozzle and purple HDPE cap.

The excipients are benzalkonium chloride, poly(vinyl alcohol), sodium chloride, sodium citrate, citric acid monohydrate, purified water, hydrochloric acid (for pH-adjustment) or sodium hydroxide (for pH-adjustment).

II.2 Drug Substance

The active substance is brimonidine tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Brimonidine tartrate is a white or slightly yellowish or slightly brownish powder. It is soluble in water, practically insoluble in anhydrous ethanol and in toluene. The particle size distribution and discussion on polymorphic forms is not relevant since the finished product is in a form of solution.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.
Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality as it in line with the monograph in the Ph.Eur. and additional specifications as mentioned on the CEP. Tests to control the microbiological quality and carry-over of residual solvents are included and validated. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for three initial, three additional and three scale-up batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 to 9 months). A retest period is not established yet.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The composition of the drug product was based on the composition of the reference product. It has been adequately shown that the test and reference product are identical with respect to their physical and chemical characteristics (e.g. pH, osmolality, viscosity, buffering capacity, specific gravity, surface tension, drop weight, benzalkonium chloride content, impurity profile and brimonidine content). The efficacy of antimicrobial preservation has been demonstrated at both the release and the proposed end of shelf-life lower limit. Manufacturing process development has been adequately described and the sterilisation method (sterile filtration) is considered justified based on the provided data of the bulk solution and requirements/limitations of the container closure system. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process has been adequately described. It consists of solution preparation, drug and buffer preparation, filtration of the solution, and filling in gamma sterilised bottles. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for six consecutive commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological attributes
The drug product is routinely tested for sterility. This is in line with the requirements for eye drops solutions of the general Ph.Eur. eye preparations monograph. Preservative efficacy down to a benzalkonium chloride content of 85% of the product specification was demonstrated.

Quality control of drug product
The final product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, filling volume, weight loss, pH, osmolality, viscosity, sub-visible particles, container-closure integrity, colour intensity, assay, related substances, sterility and efficacy of antimicrobial preservation. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data have been provided for six commercial scale batches packed in the intended 5 ml and 10 ml LDPE container. The drug product has been stored at long-term conditions (25°C/40% RH; 18 months) and accelerated conditions (40°C/25% RH; 6 months). In-use testing was performed according to the dose regimen in the SmPC during 28 days at 25°C/40% RH. At accelerated conditions (6 months), at long term conditions (18 months) and during 28 days in-use testing the batches remained within specification.
Based on the stability data provided, a shelf-life of 3 years and the proposed in-use shelf-life after first opening of 28 days can be granted without additional temperature storage conditions. The product is not considered susceptible to light degradation within the primary container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies.
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Brimonidine Warren has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:
• The MAH has committed to provide data on the efficacy of the preservatives for the finished product batch at the end of the shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Brimonidine Warren is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Alphagan which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Brimonidine tartrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Bio waiver
No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative attributes of the product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/95) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed.

Since the qualitative and quantitative composition of the product is similar to that of the reference product Alphagan 2 mg/ml eye drops, solution and the pharmaceutical properties (i.e. osmolality, pH, relative density, surface tension and droplet volume) are comparable to that of the reference product
as well, a biowaiver can be granted. Brimonidine Warren may be considered as therapeutic
equivalent, with the same efficacy/safety profile as known for the active substance of the reference
medicinal product.

IV.3 Risk Management Plan

The 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 Brimonidine Warren.

Summary table of safety concerns as approved in RMP:

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<tr>
<th>Important identified risks</th>
<th>Hypersensitivity/ocular allergy</th>
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<td></td>
<td>CNS depression in paediatrics</td>
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<td></td>
<td>Cardiac and vascular disorders</td>
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<td>Important potential risks</td>
<td>Damage to the corneal epithelium due to use of eye drops containing preservatives</td>
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<td></td>
<td>Accidental overdose/ingestion in children</td>
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<td></td>
<td>Late anterior uveitis</td>
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<td>Missing information</td>
<td>Use during pregnancy and lactation</td>
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<td>Use in patients with kidney and hepatic impairment</td>
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation
measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator
product Alphagan eye drops, solution. It is accepted that no new clinical and bioequivalence studies
were conducted, while a biowaiver was granted. Risk management is adequately addressed. This
hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the
requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test
with 2 participants, followed by two rounds with 10 participants each. The questions covered the
following areas sufficiently: traceability, comprehensibility and applicability. The results show that the
PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of
medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Brimonidine Warren 2 mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality and is
a hybrid form of Alphagan 2 mg/ml eye drops, solution. Alphagan is a well-known medicinal product
with an established favourable efficacy and safety profile.

Brimonidine Warren is a product for ocular use (eye drops) intended to act without systemic
absorption. Therapeutic equivalence with the reference product has been shown by the comparison of
the dosage form, qualitative and quantitative composition and the results of in vitro studies on the
relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Brimonidine Warren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 December 2016.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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