PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Dorzolamide 20 mg/ml PCH, eye drops, solution
Pharmachemie B.V., the Netherlands

dorzolamide (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1228/001/DC
Registration number in the Netherlands: RVG 101121

18 February 2010

Pharmacotherapeutic group: antiglaucoma preparations and miotics, carbonic anhydrase inhibitors
ATC code: S01EC03
Route of administration: ocular
Therapeutic indication: elevated intra-ocular pressure in: ocular hypertension, open-angle glaucoma, pseudo-exfoliative glaucoma; as adjunctive therapy to beta-blockers, as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated.

Prescription status: prescription only
Date of authorisation in NL: 21 October 2009
Concerned Member States: Decentralised procedure with DK, EE (withdrawn on 14 September 2009), EL, ES, FI, FR, HU, LT (withdrawn on 19 October 2009), LV (withdrawn on 15 September 2009), PL, PT, RO, SK, UK
Application type/legal basis: Directive 2001/83/EC, Article 10(1), 10(3) (only in the UK)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Dorzolamide 20 mg/ml PCH, eye drops, solution, from Pharmachemie B.V. The date of authorisation was on 21 October 2009 in the Netherlands.

The product is indicated:
- As adjunctive therapy to beta-blockers,
- As monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated,

in the treatment of elevated intra-ocular pressure in:
- ocular hypertension,
- open-angle glaucoma,
- pseudo-exfoliative glaucoma.

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

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II) found primarily in red blood cells (RBCs) but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion. The result is a reduction in intra-ocular pressure (IOP).

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra-ocular pressure is a major risk factor in the pathogenesis of optic nerve damage and visual-field loss. Dorzolamide does not cause pupillary constriction and reduces intra-ocular pressure without side effects such as night blindness, accommodative spasm. Dorzolamide has minimal or no effect on pulse rate or blood pressure.

Topically applied beta-adrenergic blocking agents also reduce IOP by decreasing aqueous humor secretion but by a different mechanism of action. Studies have shown that when dorzolamide is added to a topical beta-blocker, additional reduction in IOP is observed; this finding is consistent with the reported additive effects of beta-blockers and oral carbonic anhydrase inhibitors.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Trusopt 20 mg/ml, eye drops (NL License RVG 17618) which has been registered in the Netherlands by Merck Sharpe & Dohme since 31 January 1994. In addition, reference is made to Trusopt authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC in all member states, except for the UK, where the authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Dorzolamide 20 mg/ml PCH is a product for ocular use (eye drops) intended to act without systemic absorption, with qualitatively and quantitatively the same excipients used in the reference product, it is exempted for biostudy (Guideline CPMP/239/95 on locally applied, locally acting products, containing known constituents). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.
No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is dorzolamide hydrochloride, and established active substance described in the Ph. Eur. and USP*. The active substance is a white to off-white crystalline powder soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol. The drug substance shows polymorphism. Polymorphic form II is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Dorzolamide hydrochloride is manufactured in 4 steps. The active substance has been adequately characterized and the specifications are adequate to control the quality of the active substance.

Quality control of drug substance
The drug substance specification is based on the Ph. Eur. monograph. Additional limits are included for water content, residual solvents and microbial tests. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for two batches stored at 25°C/60%RH and 40°C/75%RH. The batches were adequately stored. Stability data up to 6 months are available. As no retest period could be granted, the active substance will be tested immediately prior to use.

* Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.

Medicinal Product

Composition
Dorzolamide 20 mg/ml PCH contains as active substance is a clear, viscous solution, free from visible particles.

The solution is packed in 5 ml fill volume capacity polyethylene bottle equipped with a dropper applicator and closed with a tamper proof cap.
The excipients are: hydroxyethyl cellulose, mannitol E421, sodium citrate E331, sodium hydroxide E524 (to adjust to an approximate pH of 5.6), benzalkonium chloride, water for injection.

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the eye drops is based on the composition of the innovator product.

No bioequivalence study is performed. This is acceptable, since the MAH has shown that critical parameters, e.g., viscosity, surface tension and drop size are similar to the innovator product. The pharmaceutical development of the product has been adequately performed.

**Manufacturing process**

First the dorzolamide partial solution is made and sterilised by filtration. Secondly the hydroxyethyl cellulose solution is sterilised by heat. These two solutions are aseptically combined and mixed. This solution is aseptically filled into sterile bottles.

The manufacturing process has been adequately validated according to relevant European guidelines. The product is not manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for three full-scale batches. The MAH committed to provide the results of the validation study of the manufacturing process on the first three production batches.

**Excipients**

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

**Container closure system**

The product at issue is packed in LDPE bottle equipped / LDPE dropper applicator / HDPE tamper proof cap as the Dutch innovator product, Trusopt, is packed in HDPE bottles according to its SPC. Dose reproducibility was compared between the product for registration and Trusopt. Both bottles/products give a comparable drop weight.

The proposed container closure system is sterilised with gamma irradiation. Before sterilisation the bioburden of dorzolamide partial solution is controlled. The low and high density polyethylene material complies with Ph. Eur.

**Quality control of drug product**

The product specification includes tests for appearance, colour, pH, osmolality, viscosity, identification of dorzolamide, assay of dorzolamide and benzalkonium chloride, related substances, particulate matter, sterility and weight loss. The release and shelf-life limits are similar, except for related substances. The proposed specification is acceptable. Polymorphism is not applicable, since the active substance is dissolved. Viscosity, osmolality and pH were based on the innovator product. Microbiological tests were carried out to ensure that dorzolamide eye drops solution is sterile.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided on three full-scale batches, demonstrating compliance with the release specification.

**Stability of drug product**

Stability data on the product has been provided for three full-scale batches. The batches were stored at 25°C/40%RH, 30°C/65%RH and 40°C/25%RH. The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in LDPE bottles/LDPE dropper and HDPE cap. The efficacy of antimicrobial preservation has been shown.

Data up to 18 months (25°C), 12 months (30°C) and 6 months (40°C) were submitted. Based on these data, a re-test period of 24 could be granted with the storage condition ‘store below 30°C. Do not refrigerate or freeze’. The MAH committed to provide stability data covering the whole shelf-life.

**In-use stability**

The product is a multi-dose preparation, therefore an in-use stability study was performed in accordance with the Guideline on In-use stability, on 2 batches for 4 weeks. The samples had been stored at 25 ± 2°C for three months prior to use.
The normal usage of dorzolamide eye drops was simulated; one drop was removed twice a day. This is the minimum daily dose. After 28 days no changes were observed. In addition, the product was still sterile and the benzalkonium content was not altered. The proposed holding time is therefore acceptable.

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.2 Non clinical aspects

This product is a generic formulation of Trusopt 20 mg/ml, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of dorzolamide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Dorzolamide is a well-known active substance with established efficacy and tolerability.

The excipients used in the manufacturing of Dorzolamide 20 mg/ml PCH eye drops, solution are the same as the already approved innovator product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/05) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. The essential physical and chemical similarity of Dorzolamide 20 mg/ml with the reference product was demonstrated and therefore the exemption from biostudy can be supported. Dorzolamide 20 mg/ml PCH may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Dorzolamide was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of dorzolamide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test
The package leaflet 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.
A total number of 20 questions were asked. 16 questions specifically addressed the key safety messages of the leaflet in a randomized order; the other 4 questions were meant to obtain a general impression of the package leaflet, including aspects as design and lay-out. It was determined whether the respondents were able to find the information and whether they understood the information and could act upon it.
A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PIL, and 90% of all participants can show that they understand and can act upon it. This criterion was met.

The overall impression of the leaflet was positive. Very few negative comments were given, and none of those were given by more than one participant. Hence, results of user consultation did not indicate a need for changing the lay-out and design.

No weaknesses of the PIL were identified, neither from the 16 questions specifically addressing the key safety issues, nor from the 4 open questions aiming to identify positive and negative impressions of the PIL (including lay-out). Therefore, no changes to the PIL were proposed.

In summary, an adequate readability testing has been documented by this report. The package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.
III  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Dorzolamide 20 mg/ml PCH eye drops, solution has a proven chemical-pharmaceutical quality and is a generic form of Trusopt 20 mg/ml eye drops. Trusopt is a well-known medicinal product with an established favourable efficacy and safety profile.

Dorzolamide 20 mg/ml PCH is a product for ocular use (eye drops) intended to act without systemic absorption, with the same excipients used in the reference product, it is exempted for biostudy.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other dorzolamide containing products.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dorzolamide 20 mg/ml PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 October 2008. Dorzolamide 20 mg/ml PCH was authorised in the Netherlands on 21 October 2009.

A European harmonised birth date has been allocated in (11 November 1994) and subsequently the first data lock point for dorzolamide is May 2010. The first PSUR will cover the period from October 2008 to May 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 January 2010.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH committed to provide the results of the validation study of the manufacturing process on the first three production batches.
- The MAH committed to provide stability data covering the whole shelf-life.
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>IOC</td>
<td>Intra-Ocular Pressure</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cells</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
<tr>
<td>Scope</td>
<td>Procedure number</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Withdrawal of the marketing authorization in Latvia on 15 September 2009.</td>
<td>NL/H/1228/001/DC</td>
</tr>
<tr>
<td>Change in the name of the marketing authorization holder in France.</td>
<td>NL/H/1228/001/IA/001</td>
</tr>
<tr>
<td>Withdrawal of the marketing authorization in Lithuania on 19-10-2009.</td>
<td>NL/H/1228/001/DC</td>
</tr>
<tr>
<td>Change in the name of the medicinal product in Spain.</td>
<td>NL/H/1228/001/IB/002</td>
</tr>
</tbody>
</table>