

Public Assessment Report

Scientific discussion

**Brinzolamide Pharmathen 10 mg/ml,
eye drops, suspension**

(brinzolamide)

NL/H/2717/001/DC

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This module reflects the scientific discussion for the approval of Brinzolamide Pharmathen 10 mg/ml, eye drops, suspension. The procedure was finalised on 18 February 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Brinzolamide Pharmathen 10 mg/ml, eye drops, suspension from Pharmathen S.A.

The product is indicated to decrease elevated intraocular pressure in:

- ocular hypertension
- open-angle glaucoma

as monotherapy in adult patients unresponsive to beta-blockers or in adult patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers or prostaglandin analogues.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Azopt® 10 mg/ml eye drops suspension which has been registered in the EEA by Alcon Laboratories (UK) Ltd since 9 March 2000 through centralised procedure EMEA/H/C/000267.

The concerned member states (CMS) involved in this procedure were Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Poland, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application because equivalence cannot be demonstrated through bioequivalence studies.

II. QUALITY ASPECTS

II.1 Introduction

Brinzolamide Pharmathen 10 mg/ml is a white homogenous suspension, with pH 7.1 – 7.9 and osmolality 270 – 320 mOsm/kg.

The suspension is packed in 10 ml dropper containers consisting of LDPE bottle with LDPE sealed dropper tip and white PP or HDPE cap with a tamper-proof seal, containing 5 ml white homogenous suspension.

The excipients are: benzalkonium chloride solution 50%, mannitol (E421), poloxamer 407, disodium edetate, carbomer 974P, sodium chloride, sodium hydroxide (for pH adjustment), water for injection

II.2 Drug Substance

Brinzolamide is a well known active substance, not described in the European Pharmacopoeia (Ph.Eur.). However, a monograph in the United States Pharmacopoeia (USP) is available. The substance is a white or almost white non-hygroscopic powder, which is slightly soluble in alcohol and in methanol and insoluble in water. Further, brinzolamide exhibits isomerism; the isomer produced is the R-isomer. The active substance does not exhibit polymorphism.

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/EMA 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

A suitable description of the process has been provided. The starting materials have been adequately defined and are acceptable.

Quality control of drug substance

The specification limits fixed by the MAH are in general set according to the European Pharmacopeia and ICH guidelines. The specification is considered to be acceptable. The S-isomer is adequately controlled.

Batch analysis results have been provided by the MAH for two batches, showing compliance to the proposed specification.

Stability of drug substance

Stability data for production-scale batches stored at 25°±2°C/60±5%RH (up to 36 months) and 40°±2°C/75±5%RH (6 months). Based on the provided data the proposed re-test period of the drug substance of 36 months is acceptable, with the following storage conditions: "Store in the original package in order to protect from light. Preserve in well closed containers".

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, and the function of the excipients explained. The chosen excipients are almost identical to the composition of the originator with the exception of the originator's tyloxapol, for which poloxamer 407 is used instead.

The enantiomeric form used is the R-isomer. A small amount of the S-isomer is formed during autoclaving. The amount is dependent on the time/temperature exposure of the solution and is controlled in the finished product, which is toxicologically qualified.

The MAH has performed an *in vivo* non-inferiority study to rule out any differences between the test and reference product. Since the drug product is a suspension, the particle size of the drug substance in the drug product is one of the key parameters that can affect *in vivo* performance. This parameter is controlled as in-process control. The proposed limits for particle size in the drug product specification are acceptable. Further pH, tonicity, viscosity and surface tension are identified as key factors affecting ocular absorption. In the comparative profiles between proposed product and the originator, it is demonstrated that these factors are similar. The MAH also has provided data to demonstrate that the drop volume is based on the average drop volume of the reference product.

Manufacturing process

The manufacturing process consists of the following steps:

- Preparation of milling mixture. Sterilization by autoclaving, followed by aseptic milling
- Preparation of vehicle solution. Sterilization by autoclaving
- Aseptic addition of milling mixture to vehicle solution
- Filling (aseptic)
- Secondary packaging.

The manufacturing process is adequately described. Process validation data have been provided from two sites, and for three commercial size batches per site. All parameters tested complied with the pre-set limits.

Control of excipients

The excipients used and their quantities are common for this type of formulation. Analytical procedures for all the excipients are performed as per requirement specified in the Ph.Eur. These specifications are acceptable.

Microbiological attributes

The product is a sterile product. Preservative effectiveness has been shown when tested towards the end of shelf life according to Ph.Eur. 5.1.3. This is acceptable.

Quality control of drug product

The product specification includes tests for appearance, extractable volume, average drop volume, relative density, pH, viscosity, osmolality, identification and assay of brinzolamide, benzalkonium chloride assay, EDTA assay, related substances and enantiomeric purity, sterility, leaker test or tightness of vials and packaging. The analytical methods have been adequately described and

validated. Batch analytical data from three commercial-scale batches has been provided. All batches comply with the proposed specification.

Stability of drug product

The following stability data on the product has been provided for three commercial scale batches: at long term and intermediate conditions 36 and 12 months data respectively are available, while at accelerated storage conditions 6 months data are provided. From a second manufacturing site additional stability data have been provided for three batches of commercial scale: 9 months data are available at long term, intermediate and 6 months at accelerated conditions. The conditions used in the stability studies are according to the ICH stability guideline. Furthermore, a water loss study was performed, as well as an in-use stability study and photostability study.

From the data it is observed that the product remains relatively stable throughout the testing period, and no storage conditions related to moisture or light sensitivity are necessary. Based on the available data, a shelf life of 36 months can be granted. The stability data from the second site confirm that the stability of the product from both sites is comparable.

In-use stability was tested in a four week study. Four drops were removed daily from the LDPE ophthalmic dispenser. Based on the results, an in-use shelf life of 4 weeks after first opening can be granted.

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 Brinzolamide Pharmathen 10 mg/ml, eye drops, suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Brinzolamide Pharmathen is intended for 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 Azopt, 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

Brinzolamide 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 reference is made to the clinical experience with the innovator product.

IV.2 Pharmacokinetics

For this hybrid application a biowaiver was initially requested. A biowaiver may be applied for ophthalmic solutions. However, the current product as well as the innovator Azopt, is formulated as a suspension. Being a suspension, it cannot be ruled out that absorption and distribution into and from the eye are different between the test product and innovator. Differences may affect efficacy and safety. Therefore a pharmacodynamic or clinical study is required to show therapeutic equivalence according to the 'Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents'.

IV.3 Clinical efficacy and safety

As requested the MAH submitted a randomized, double-blind non-inferiority study to compare the proposed product Brinzolamide Pharmathen 10 mg/ml (Pharmathen S.A., Greece) with the reference product Azopt 10 mg/ml eye drops suspension (Alcon Laboratories UK Ltd). These products differ with respect to a non-ionic wetting agent: poloxamer 407 for the test product versus tyloxapol for the reference product. All other ingredients of both products (active and non-active) are essentially similar according to the MAH. The MAH also declared that all physicochemical properties are essentially similar.

Objectives

The primary objective of the prospective, randomized, double-blind parallel phase III study was to evaluate the non-inferiority of proposed eye drop solution containing Brinzolamide 10 mg/ml (test product) as compared to a reference product (Azopt® 10 mg/ml eye drops suspension) for the treatment of elevated intraocular pressure (IOP) or open angle glaucoma. The secondary objective was to compare the overall efficacy and safety of the two Brinzolamide products (test and reference) in subjects with open angle glaucoma or ocular hypertension in at least one eye.

Design

One-hundred and sixty-nine (169) adult male and female subjects with open angle glaucoma or ocular hypertension in at least one eye were included in the present trial; 88 patients received test treatment and 81 patients reference treatment. The mean age \pm standard deviation was 63.1 ± 11.3 years for patients who received test treatment and 63.2 ± 13 for patients who received reference treatment. In the test group, 39.8% of patients were men compared to 37.0% of patients in the reference group. The subjects were randomized in permuted blocks of four. A washout period was applied in case patients received other (ophthalmic) medications.

During a treatment period of 12 weeks, all subjects received daily administrations of 2 eye drops into the conjunctival sac: once in the morning and once in the evening, approximately 12 hours apart. Study patients recorded date and time of each installation in a diary. The chosen dosage of one drop in each eye two times a day corresponds to the dosage recommendation of the reference product.

After the screening visit, 4 study visits were planned during the 12-week treatment period. At each visit, intraocular pressure (IOP) measurements were performed by means of a calibrated Goldmann tonometer at 8:00 am, noon, and 4:00 pm. IOP was measured in each eye, at each visit, and at each time point twice per eye and each value was documented. If both measurements of the same eye differed by more than 4 mmHg, a third measurement was performed and documented. Blood samples were drawn for the analysis of brinzolamide at the screening visit and end of study visit.

The primary endpoint was the reduction in IOP at 8:00 a.m. upon test or reference treatment, characterized as an intra-individual difference in the target eye from baseline to the end of the treatment period (12 weeks). The target eye was defined as the eye with the higher IOP. If both eyes had the same IOP, the investigator selected the target eye, using a right/left assignment. Statistical analysis was performed on the full analysis set without imputation as well in the per protocol population (all study patients who completed the double-blind treatment period).

The study design is considered appropriate to determine the effects of the test and reference eye drop suspension. The duration of treatment period is considered long enough to determine the IOP lowering effects of the test and reference brinzolamide eye drop suspension, since brinzolamide has been shown to achieve maximum inhibitory activity for the carbonic anhydrase type II isozyme within 2 to 4 weeks.

Efficacy results

One hundred sixty-nine patients were included in the study and received study treatment after randomization. Thirty-one patients discontinued study participation prematurely (test treatment: 8 (9.1%); reference treatment: 23 (28.4%)). This appeared to be largely due to difference in protocol violations (14 patients upon reference treatment compared to 4 patients upon test treatment), which occurred by chance more frequently in the reference group. Baseline Intra ocular pressure (mean ± SD) for test and reference was 25.5 ± 2.2 mmHg and 25.7 ± 2.2 mmHg, respectively

Efficacy results are represented in the table below.

Table 1. Reduction in intraocular pressure at each study visit as compared to pre-treatment evaluation (randomization visit) (full analysis set).

	Test – Reference Brinzolamide solution	95% Confidence Intervals	
		Lower Limit	Upper Limit
2 weeks of treatment	0.43	-0.90	1.75
6 weeks of treatment	0.36	-1.12	1.83
12 weeks of treatment	0.45	-0.75	1.66

The mean reduction difference in IOP between test and reference treatment was 0.45 (95% confidence interval -0.75 to 1.66). The MAH set the non-inferiority margin to -1.5 mmHg, which should have been -1 mmHg instead. However, also when the non-inferiority margin of -1 mmHg is applied, the test Brinzolamide Pharmathen 10 mg/ml can be considered non-inferior to the reference product.

Safety results

In the test group 28.4% patients reported adverse events, compared to 14.8% of patients who received the reference brinzolamide eye drops suspension. The observed higher rate of adverse events in the test group as compared to the reference group is not statistically significant, and the majority of adverse events in the test group were considered not or unlikely related to the study drug. With the exception of abnormal laboratory parameters, the adverse events were relatively balanced between the treatment groups. Therefore it can be concluded that the safety of the proposed product is acceptable.

Absolute proportional differences between the proposed and reference brinzolamide 10 mg/ml ophthalmic suspension were especially large with respect to investigations (13.6% vs. 3.7% respectively). The observation rates of hyperglycemia and abnormal liver function tests tended to be higher upon use of the proposed Brinzolamide Pharmathen 10 mg/ml suspension compared to the reference product Azopt. However these were found to be partially related to other factors such as concomitant medication and other pathology. It is considered that these abnormalities are not clinically significant.

Conclusion

The results of the study show that the efficacy of Brinzolamide Pharmathen is non-inferior to the reference product Azopt 10 mg/ml eye drops suspension for the treatment of subjects with open angle glaucoma or ocular hypertension. In terms of safety the products can be considered similar.

IV.4 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 Brinzolamide Pharmathen 10 mg/ml, eye drops, suspension.

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Corneal decompensation • Metabolic acidosis • Interaction with ocular hypotensive agents
Important potential risks	<ul style="list-style-type: none"> • Cardiovascular disorders • Interaction with oral CAIs • Interaction with salicylates • Long term use of preserved eye drops
Missing information	<ul style="list-style-type: none"> • None

The summary of the RMP is acceptable, since it is in line with the summary of safety concerns for the reference product Azopt. Routine risk minimisation measures are sufficient for all safety concerns. No additional activities are required.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Azopt 10 mg/ml eye drops, suspension. The MAH demonstrated through a clinical study that Brinzolamide CF is non-inferior to the reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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. Twenty-four (24) participants were tested in total. Four (4) participants were tested during the preliminary round of testing. Ten (10) participants were tested in the first round and ten (10) participants were tested in the second round. Both in the first and the second round, for each question, 90% of all participants were able to find the information requested within the PL, and 90% of all participants could show that they understand and can act upon it. The results of this test indicate that the PL is well structured and organised, easy to understand and written in a comprehensible manner, and meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Brinzolamide Pharmathen 10 mg/ml eye drops suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Azopt® 10 mg/ml eye drops suspension. Azopt is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are suspensions, it cannot be ruled out that absorption and distribution into and from the eye would be different between the test product and innovator. Therefore a non-inferiority study was conducted, showing satisfactory results.

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 non-inferiority has been demonstrated for Brinzolamide Pharmathen 10 mg/ml eye drops suspension compared to the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 February 2015. In the Netherlands the marketing authorisation was granted on 13 April 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/non approval	Assessment report attached