CBG MEB

# Public Assessment Report

# Scientific discussion

# Brinzolamide Sandoz 10 mg/ml, eye drops, suspension

# (brinzolamide)

# NL/H/2900/001/DC

# Date: 18 November 2014

**This module reflects the scientific discussion for the approval of Brinzolamide Sandoz 10 mg/ml, eye drops, suspension. The procedure was finalised on 25 May 2014. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

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

The product is indicated for 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 EU.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, Malta, Norway, Poland, Portugal, Slovakia, Spain, Sweden 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 Sandoz 10 mg/ml is a white to off-white suspension, pH 7.1 – 7.9 and osmolality 270 – 320 mOsm/kg.

The suspension is packed in LDPE bottles with LDPE dropper with e PP tamper-proof screw cap.

The excipients are: benzalkonium chloride, disodium edetate, mannitol (E421), carbomer 974P, tyloxapol, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

## II.2 Drug Substance

The active substance is brinzolamide, an established active substance described in the United States Pharmacopoeia (USP). It appears as white to off-white powder or crystals. The aqueous solubility is pH dependent with minimal solubility at neutral pH and increased solubility at more basic or acid pH. The compound has a single chiral centre that has been established as having the R-configuration.

Manufacturing process
Brinzolamide is produced by two manufacturers using a validated stereoselective process, which proceeds in either four steps or eight steps, including final purification.

Quality control of drug substance
The routine controls and established specifications include description, identification, solution colour and clarity. None of the specified impurities have been detected as degradants in the finished product, except for the S-isomer. This isomer is adequately controlled.
Results of several production scaled batches have been presented manufactured at both sites. All batches manufactured according to the optimised procedure meet the specifications. The results presented support the quality level established and confirm the consistency and uniformity of the manufacturing process.

Stability of drug substance
For one manufacturer long-term stability data for 7 batches and accelerated stability data for 3 batches have been provided, confirming a retest period of 4 years.
For the second supplier long-term and accelerated stability data for 3 batches and long-term stability data for 5 additional lots have been provided, confirming the 2 year retest period.

## II.3 Medicinal Product

Pharmaceutical development
The objective of the pharmaceutical development was to develop a stable, well-preserved 1% sterile suspension dosage form. The MAH has declared that qualitative and quantitative composition, the production site, the manufacturing procedure and the source of the active substance are identical to the Azopt dossier.
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.
A suspension dosage form is justified and in line with the innovator. It is not possible to terminally sterilise the product in the final container. Hence aseptic ball milling of a sterile autoclaved slurry of brinzolamide is performed, using zirconium alloy beads. No overages are applied. Only one polymorphic form of brinzolamide has been observed and there are no polymorphic changes during manufacturing. Regarding drop size no comparison with the reference product has been made. However, this should be considered the same as the same manufacturing process (and container closure) are used.

Manufacturing process
The manufacturing process is composed of five major steps. It includes preparation of the milling slurry, steam sterilisation followed by aseptic milling, sterile filling into sterilised packaging and secondary packaging. The manufacturing process has been described in sufficient detail regarding times, temperatures and sterilisation procedures. The steam sterilisation is performed according to Ph.Eur. conditions. Further processing is performed under aseptic conditions. This process has been sufficiently justified.
The manufacturing process is considered a non-standard process, as the product is a suspension, partly prepared by aseptic techniques. Validation results have been provided on a number of batches. The provided data is considered sufficient for the validation of this process.

Control of excipients
All the excipients used in the manufacture of the drug products are of European Pharmacopoeia (Ph.Eur.) quality, except tyloxapol, which is of USP quality. Certificates of analysis of all excipients are presented, which are in accordance with the proposed specifications.

Microbiological attributes
The product is a sterile product. Preservative effectiveness has been shown at release and during storage. Eye drops containing only 80% of label primary preservative benzalkonium chloride also showed preservative effect. The shelf-life limit is acceptable.

Quality control of drug product
The finished product specifications include tests for appearance, identification, brinzolamide assay, benzalkonium chloride identity and assay, disodium edetate dihydrate identity and assay, pH, osmolality, resuspendability, viscosity, sterility (EP), and fill volume.
Particle size distribution is important. A validated method for measuring the suspension particle size has been developed. Specifications concerning particle size are in accordance with Ph.Eur. for this type of compound. Batch analysis results of several batches comply with the specifications.

Stability of drug product
Stability data of three batches of commercial size were presented. The longest duration was 3 years at 25°C/40% RH. In addition to the stability study, historical data and data at 40°C and 30°C, photostability and thermal cycling has been provided.

The stability data show that the product is chemically, physically, and microbiologically stable for 2

years in the packaging sterilised with ethylene oxide and/or gamma irradiation. A slight photodegradation was observed. The efficacy of the antimicrobial preservative has been shown in this period. No specific storage condition is considered necessary (temperature or light).

Once opened, a 28-day in-use period is justified on microbiological grounds. In addition an in-use study of chemical parameters was conducted on two batches, which have been stored at long-term storage condition (25°C/35% RH) for 2 years. After 28 days, the product samples were tested for chemical as well as physical parameters. The proposed 28 days in-use shelf life is justified and acceptable, and is reflected in the SmPC.

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 Sandoz 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 Sandoz 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 there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

### IV.2 Pharmacokinetics

Biowaiver
No bioequivalence studies have been submitted to support the application. The applicant clarified that Brinzolamide Sandoz 10 mg/ml, eye drops, suspension has the same qualitative and quantitative composition in terms of the active substance, excipients and the same pharmaceutical form, is manufactured in the same sites and follows the same manufacturing process as the reference product

AZOPT® 10 mg/ml eye drops suspension. The member states therefore agreed with that no bioequivalence studies are considered necessary.

### 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 Brinzolamide Sandoz.

| Summary of safety concerns | |
|---|---|
| Important identified risks | Corneal Decompensation in patients with compromised corneas |
| | Metabolic Acidosis |
| Important potential risks | Cardiovascular Disorders |
| | Long - Term Use of Preserved Eye Drops |
| Important missing information | 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.4 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. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

A bridging study was performed to bridge the package leaflet (PL) for Brinzolamide Sandoz 10 mg/ml with the approved product, AZOPT® 10 mg/ml eye drops suspension marketed by Alcon Laboratories (UK) Ltd. The MAH has established a corporate PL layout, which has been tested in more than 50 readability tests on products of the MAH. The well established PL layout will be used for the final version of the PL of Brinzolamide Sandoz 10 mg/ml, eye drops, suspension. The bridging study shows that the PLs of Brinzolamide Sandoz 10mg/ml eye drops suspension and the approved product, AZOPT® 10mg/ml eye drops suspension are highly similar. No separate user testing is required.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

No bioequivalence study is deemed necessary. 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Brinzolamide Sandoz 10 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 May 2014.

## 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 |
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