LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Brintidox
(brinzolamide and timolol maleate)

SE/H/1983/01/DC

This module reflects the scientific discussion for the approval of Brintidox. The procedure was finalised on 2019-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Brintidox, 10 mg/ml / 5 mg/ml, eye drops, suspension, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. Doc Generici S.r.l., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is AZARGA, 10mg/ml + 5mg/ml, eye drops, suspension authorised in EU since 2008, with Novartis Europharm Ltd. as marketing authorisation holder.

The reference product used in the bioequivalence study is AZARGA, 10mg/ml + 5mg/ml, eye drops, suspension from Germany with Novartis Europharm Ltd. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new non-clinical studies were submitted to support the application.

III.2 Pharmacology, pharmacokinetics and toxicology

Brinzolamide and timolol decrease elevated IOP primarily by reducing aqueous humour secretion as further described in the SmPC.

The pharmacodynamic, pharmacokinetic and toxicological properties of brinzolamide and timolol are well-known. Brinzolamide and timolol are widely used, well-known active substances, and the applicant has provided a review of published relevant literature.

The excipients used are well-known and raise no cause for concern.

III.3 Ecotoxicity/environmental risk assessment

An ERA phase I PEC calculation has been performed. The calculated $PEC_{surface\ water}$ of brinzolamide and timolol are both below 0.01 µg/L. It is therefore assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant submitted one original clinical study developed to compare Brinzolamide/Timolol to the originator Azarga, including a review of published relevant literature.

IV.2 Pharmacokinetics

No pharmacokinetic study was performed in humans since the systemic exposure is expected to be similar to the reference product. The compounds included in the FDC are well-known, however the test product does not include any surfactant, which is included in the reference product. Accordingly, a clinical study was performed to evaluate the efficacy and safety of the test product compared to the reference product.

IV.3 Pharmacodynamics

No new data were provided. Pharmacodynamics is appropriately described in the SmPC.

IV.4 Clinical efficacy

The combination brinzolamide/timolol is well known to have a relevant IOP lowering effect for treatment in patients with of open-angle glaucoma or ocular hypertension for whom

monotherapy provides insufficient IOP reduction. The applicant provided an appropriate review of published literature.

The current application concerns a new FDC of brinzolamide/timolol with the same composition of active ingredient as the already approved brinzolamide+timolol, Azarga,apart from the surfactant which is not included in the test product. A clinical study was submitted to establish a bridge between the test product and the reference product Azarga.

Study AZ07 was a Phase III, Multicentre, Randomised, Investigator-masked, Crossover, Comparative Clinical Trial Evaluating the Efficacy and Safety of the Generic Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops Suspension (test product) with Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops Suspension Azarga® (Alcon Ltd), with open angle Glaucoma and Ocular Hypertension. All patients had elevated IOP / primary open angle glaucoma in at least one eye: mean diurnal IOP pre-treatment equal or higher than 22 mmHg, and equal or lower to 35 mmHg (untreated, i.e. naïve or after washout).

Descriptive statistics was used to summarise IOP at Day 1 and Day 22 using the mean of the 3 time points (08.00, 10.00 and 16.00 o' clock).

To address a potential carry over effect in the crossover design, results on sequence and period effect were presented, which did not indicate a sequence or period effect.

In conclusion, overall, the benefit of test product appears to be positive in patients with ocular hypertension to the same extent as the reference product.

IV.5 Clinical safety

The most frequently reported adverse events in the Brinzolamide/Timolol test product group were blurred vision. There was also reporting of dysgeusia; headache; eye discharge; and eye pain.

Since the surfactant was removed from the test product, compared to the reference product, no new safety findings for the test product were anticipated. The observed differences in AE reporting may be a chance finding due to the limited size of the safety database.

Generally, overall, no ocular or systemic adverse events were identified that have not been already well documented with the reference product, as described in the SmPC of Azarga.

IV.6 Risk Management Plans

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 Brintidox.

The updated Safety concerns for Brintidox, are in line with the reference product Azarga.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, is considered acceptable.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Azarga, EMEA/H/C/960 (content) and Brinzaflux, NL/H/2717/001/DC (layout). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and the product information is acceptable. Brintidox, 10 mg/ml + 5 mg/mL eye drops, suspension is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Description	Due date
Validation of analytical method for viscosity, including discriminatory ability of the method	2020-06-30

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Brintidox, 10 mg/ml + 5 mg/mL eye drops, suspension, was positively finalised on 2019-12-11.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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