COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Brinzolamide/Timolol Mylan 10+5 mg/ml, eye drops, suspension (brinzolamide and timolol maleate)

NL/H/5554/001/DC

Date: 23 September 2022

This module reflects the scientific discussion for the approval of Brinzolamide/Timolol Mylan 10+5 mg/ml, eyedrops, suspension. The procedure was finalised on 11 December 2019 with Sweden as RMS (SE/H/1982/01/DC). The current RMS is the Netherlands (NL/H/5554/001/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IOP	Intraocular pressure
MAH	Marketing Authorisation Holder
PEC	Predicted environmental concentration
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for the fixed-dose combination Brinzolamide/Timolol Mylan, 10+5 mg/ml, eye drops, suspension, from Mylan Pharmaceuticals Limited.

The product is indicated for decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction (see section 5.1 of the SmPC).

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 Azarga 10mg/ml + 5mg/ml eye drops, suspension, which has been registered in the EU by Novartis Europharm Limited since 2008. In the Netherlands, Azarga has been registered since 25 November 2008 by central procedure EU/1/08/482.

The reference member state (RMS) of the initial procedure was Sweden and the concerned member states (CMS) involved in this procedure were Estonia, France, Italy, Latvia, Lithuania, the Netherlands and the United Kingdom. The role of RMS was transferred to the Netherlands on 23 November 2021.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. This concerns a hybrid application, as no surfactant is included in the test product compared to Azarga.

II. QUALITY ASPECTS

II.1 Introduction

Brinzolamide/Timolol Mylan is a white to off-white uniform suspension, pH 7.2 (approximately). One ml of suspension contains 10 mg brinzolamide and timolol maleate corresponding to 5 mg timolol.

The suspension is packed in 5 ml low density polyethylene (LDPE) bottle, with a LDPE insert dropper and a high density polyethylene (HDPE) cap containing 5 ml suspension.

The excipients are: benzalkonium chloride, mannitol (E421), carbomer, disodium edetate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and purified water.

II.2 Drug Substance

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

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

Quality control of drug substance
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 of drug substance
Stability studies confirm the retest period.

II.3 Medicinal Product

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

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

Quality control of drug product
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 of drug product
Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the SmPC, 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 MAH 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 (ERA)

An ERA phase I Predicted environmental concentration (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 MAH 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 fixed-dose combination 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 MAH provided an appropriate review of published literature.

The current application concerns a new fixed-dose combination 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 Limited), 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 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/Timolol Mylan.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the MAH, 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

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 language used for the purpose of user testing the PL was English.
The results show that the PL 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/Timolol Mylan 10+5 mg/ml, eye drops, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Azarga 10mg/ml + 5mg/ml eye drops, suspension. Azarga is a well-known medicinal product with an established favourable efficacy and safety profile.

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/Timolol Mylan

with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 December 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval / non approval	Summary/ Justification for refuse
NL/H/5554 /001/IA/006	B.III.1.a)2 Updated certificate from an already approved manufacturer	N	25 March 2022	Approval	
NL/H/5554 /001/IA/008	C.I.3. a) Implementation of wording agreed by the competent authority	Y	16 September 2022	Approval	