CBG MEB

Public Assessment Report

Scientific discussion

Optilamid 10 mg/ml, eye drops, suspension

(brinzolamide)

NL/H/2833/001/DC

Date: 8 July 2015

This module reflects the scientific discussion for the approval of Optilamid 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 Optilamid 10 mg/ml, eye drops, suspension from Pharmaceutical Works Polpharma 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, Latvia, Lithuania, Poland and Romania.

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.

The MAH requested scientific advice in the Netherlands in June 2011 concerning the acceptability of the proposed therapeutic equivalence study. The advice of the MEB was followed.

II. QUALITY ASPECTS

II.1 Introduction

Optilamid 10 mg/ml is a white to off white homogenous suspension, with pH 7.3 – 7.7 and osmolality 250 – 300 mOsm/kg.

The suspension is packed in 5 ml (LDPE) bottle, containing 5 ml of eye drops, suspension, with a (LDPE) insert dropper and a (HDPE) cap.

The excipients are: benzalkonium chloride, mannitol (E421), carbomer 974P, disodium edetate, sodium chloride, purified water, hydrochloric acid/sodium hydroxide (for pH adjustment).

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 are in general set according to the European Pharmacopoeia, ICH guidelines and USP. The MAH applies the specification of the ASMF holder.
Batch analysis results have been provided for three batches showing compliance to the proposed specification.

Stability of drug substance
At present there are insufficient stability data to grant a retest period. The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 Azopt with the exception of the originator's tyloxapol, for which the applicant uses no alternative. During development, the composition was optimised until the final formulation was obtained. The particle size of the drug substance is one of the key parameters that can affect *in vivo* performance. A detailed comparison of the particle size distribution of the test and reference product has been provided.
The formulation development has been adequately performed. Since there is a difference in the qualitative composition of the test and reference product no similarity can be claimed based on the *in vitro* data. A comparative clinical study has been performed. The physicochemical and biological properties, i.e. pH, osmolality are within the physiological range. The small differences in physicochemical parameters data between test and reference products are not considered relevant, considering the clinical study performed. The viscosity and re-suspendability limits have been discussed during the drug product development and are acceptable. The MAH adequately demonstrated that the packaging from test and innovator product deliver a comparable drop size.

Manufacturing process
During the manufacturing process, a gel mixture and a sterile suspension are prepared. The gel is separately sterilised in an autoclave. The mixture and the suspension are thereafter mixed, however not further sterilised. As autoclaving in the final container is not suitable, the individual components are pre-sterilised followed by aseptic compounding and filling. The process is adequately described.
The manufacturing process is validated on three commercial size batches. All parameters tested complied with the pre-set limits and no unexpected results were observed.

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

Microbiological attributes
Optilamid 10 mg/ml is a sterile product The sterility method has been adequately described, and the efficacy of the preservative has been adequately demonstrated. It was demonstrated that the preservative concentration at the lower specification limit in the drug product complies with the requirements of Ph.Eur. 5.1.3. This is acceptable.

Quality control of drug product
The product specification includes tests for appearance, re-suspendability, pH, viscosity, particle size, osmolality, identification and assay of brinzolamide, benzalkonium chloride and disodium edetate, related substances, volume in container and sterility. The proposed limits are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from 4 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 four commercial scale batches: at long term and intermediate conditions up to 24 months and 12 months data are available, respectively, while at accelerated storage conditions data up to 6 months are provided. The conditions used in the stability studies are according to the ICH stability guideline. From the data it is observed that the product remains stable throughout the testing period, and no storage conditions related to moisture or light sensitivity is considered to be necessary. Based on the available data, a shelf life of 2 years has been granted.

The MAH provided results from an in-use study demonstrating that the product remains stable during the in-use period. The daily dose removal of two drops was performed in laboratory environment.
Based on the results, an in-use shelf life of 4 weeks after first opening has been 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 Optilamid 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.

The following post-approval commitment has been made:

- The MAH committed to test the drug substance prior to its use in the manufacture of the product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Optilamid 10 mg/ml eye drops, suspension 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

Both Optilamid and the innovator Azopt are 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 product. Differences may affect efficacy and safety. Therefore a clinical study has been submitted 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

The MAH submitted a randomized, crossover therapeutic equivalence study to compare the proposed product Optilamid 10 mg/ml eye drops, suspension (Pharmaceutical Works Polpharma S.A., Poland) with the reference product Azopt® 10 mg/ml eye drops suspension (Alcon Laboratories UK Ltd). The difference in the composition of these eye drops, suspensions is that surfactant tyloxapol is not present in the test Optilamid 10 mg/ml eye drops, suspension.

Objectives
The primary objective of the multicentre, randomized, investigator-masked cross-over trial was to evaluate the efficacy of the proposed Optilamid 10 mg/ml (test product) as compared to the reference product (Azopt® 10 mg/ml eye drops suspension) in lowering intraocular pressure (IOP).

The primary endpoint was difference in the mean diurnal IOP in the study eye between baseline and day 29.

Secondary objectives of this trial were:
- to compare the tolerance of the test and reference products by ocular discomfort assessment in both eyes
- to compare the levels of conjunctival hyperaemia induced by the test product and reference product in both eyes
- to evaluate the general safety of the test product compared to the reference product.

The study objectives are considered appropriate for this type of application. A treatment period of 28 days is considered long enough to determine efficacy and safety of the test product.

Design
Adult patients with elevated intraocular pressure either due to primary open-angle glaucoma or ocular hypertension were eligible for inclusion. The mean age ± standard deviation was 64.5 ± 12.71 years. Sixty-one patients with IOP (mean baseline 23.5 (standard deviation 1.8) mmHg) were included in the study, received study treatment after randomization and completed the study.
After screening the patients underwent a 4 to 6 weeks wash-out period, depending on prior glaucoma-related treatment. Patients were randomly assigned to start treatment either with the test product or with the reference product or vice versa. On day 1 of any treatment period, the IOP was measured at -12, -8, -4 and 0 hours prior to dosing. Patients were instructed to apply one drop of the product into the affected eye(s) twice a day, every 12 hours between 07:00 to 10:00 and 19:00 to 22:00. The patients were instructed to fill in every brinzolamide administration on a diary card. Follow-up visits were scheduled on day 14 and day 29 in both treatment periods.

On day 14 of treatment, IOP, and occurrence of any conjunctival hyperaemia and ocular discomfort were determined. If the IOP was higher than 35 mmHg in either eye the patient had to be withdrawn from the study. Diary cards were reviewed for compliance and potential adverse events.

The duration of each treatment period was 4 weeks. The duration of the washout period was also 4 weeks.

On day 29, the IOP measurements using Goldmann applanation tonometry were done at 0, 4, 8 and 12 hours, post last dosing to determine the primary endpoint: the difference in the mean diurnal IOP in the study eye between baseline and day 29. The lower and upper difference margin for the difference in treatment effect between the test and reference product was set to 1 mmHg. Diary cards were reviewed for adverse events and compliance.

The study design is considered appropriate to determine the effects of the test and reference eye drops suspensions. The duration of treatment period is considered long enough to determine the IOP lowering effects of the test and reference brinzolamide eye drops, suspensions, since brinzolamide has been shown to achieve maximum inhibitory activity for the carbonic anhydrase type II isozyme within 2 to 4 weeks. The duration of the washout period in between the two different treatment phases is therefore also considered to be long enough to avoid the occurrence of carry-over effects.

The set lower and upper difference margin of 1 mmHg is considered appropriate.

Efficacy results

Sixty-four patients received study treatment after randomization. Three patients discontinued study participation prematurely (one patient lost to follow-up; 2 patients withdrew their consent). The remaining 61 patients are considered the intention-to-treat population. Six patients were excluded due to protocol deviations, leading to a per protocol collective of 55 patients.

Efficacy results are represented in the tables below.

Table 1. Mean difference between test and innovator Brinzolamide ophthalmic suspension (n=61 patients).

Intra-ocular pressure	**Intra-ocular pressure (mean (standard deviation))**	
	Test Brinzolamide eye drops, suspension	Reference Brinzolamide eye drops, suspension
Baseline	23.3 (1.9)	23.6 (1.8)
Day 14	19.0 (2.9)	19.3 (3.2)
Day 29	18.7 (2.7)	18.4 (2.7)
Difference day 29 and baseline	4.6 (2.6)	5.2 (2.9)
Difference (95% confidence interval)	-0.3 (-0.79 ; 0.18)	

Table 2. Pairwise comparisons

Treatment - treatment	**Mean difference**	**Std. error**	**95% confidence interval for difference** Lower bound - upper bound	
Optilamid - Azopt	-0.327	0.220	-0.767	0.113
Azopt - Optilamid	0.327	0.220	-0.113	0.767

There was no evidence for a treatment x period interaction, sequence- or cross-over effect.

In 61 out of 64 patients in the intention-to-treat population, the mean IOP reduction was 4.6 ± 2.6 mmHg for the test Optilamid 10 mg/ml ophthalmic suspension and 5.2 ± 2.9 mmHg for the reference Brinzolamide ophthalmic suspension after 28 days of treatment. This is comparable to the published IOP reduction range of 2.7 to 5.7 mmHg for Azopt® 10 mg/ml ophthalmic suspension.
In the per-protocol population (n=55), the difference in IOP lowering effect between the two investigational products was not significant (p-value 0.207 > 0.05) and the lower limit of the confidence interval was within the non-inferiority/non-superiority margin (-0.788 > -1).

Safety results

No serious adverse events have been reported. 87.5% and 84.4% of the patients reported no adverse events when treated with test product or reference product, respectively.

Thirty-seven (37) non-serious adverse events were reported by 13 patients in 18 treatment periods (14.1%) during the study (safety population: n= 64 patients, n=128 treatment periods). Twenty-three (23) of these adverse events were of ocular origin, whereas 14 were of systemic origin. Adverse

events that occurred in 3 or more per cent of patients during either test or reference treatment, were: tearing eyes, headache, blurred vision, vertigo, and eye lid stinging.
Eleven (11) adverse events occurred upon use of the reference suspension compared to 12 adverse events upon use of the test product. Most adverse events (10 adverse events for the test product and 11 adverse events for the reference product) were reported to be possibly related to the investigational products.

The minor difference in the incidence of adverse events was not statistically significant. The ocular discomfort level after application of test Brinzolamide 10 mg/ml ophthalmic suspension was lower compared to the reference Brinzolamide ophthalmic suspension.

Conclusion
The results of the study show that Optilamid is therapeutically equivalent 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 Optilamid 10 mg/ml, eye drops, suspension.

- Summary table of safety concerns as approved in RMP

Important identified risks	corneal decompensation metabolic acidosis
Important potential risks	cardiovascular events long term use of preserved eye drops
Important missing information	-

The summary of the RMP is acceptable. 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 Optilamid is therapeutically equivalent to the reference product. Risk management is adequately addressed. The concerned product is approved on the basis of a hybrid application and 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. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet 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

Optilamid 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 and innovator product. Therefore a therapeutic equivalence study was conducted, showing satisfactory results.

In the Board meeting of 5 February 2015 the available stability data on the drug substance were discussed. The Board expressed its positive position on this application, provided that the active substance will be tested prior to its use in manufacture of the product.

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 therapeutic equivalence has been demonstrated for Optilamid 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.

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