CBG MEB

Public Assessment Report

Scientific discussion

Azelastinehydrochloride Regiomedica 0.5 mg/ml, eye drops, solution, single dose container

(azelastine hydrochloride)

NL/H/2860/001/DC

Date: 22 December 2015

This module reflects the scientific discussion for the approval of Azelastine-hydrochloride Regiomedica 0.5 mg/ml, eye drops, solution, single dose container. The procedure was finalised on 17 March 2015. 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
BAC	Benzalkoniumchloride
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
MAH	Marketing Authorisation Holder
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 Azelastinehydrochloride Regiomedica 0.5 mg/ml, eye drops, solution, single dose container from Regiomedica GmbH.

The product is indicated for:
- Treatment and prevention of the symptoms of seasonal allergic conjunctivitis in adults and children aged 4 years and older.
- Treatment of the symptoms of non-seasonal (perennial) allergic conjunctivitis in adults and children aged 12 years and older.

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 Optilast Eye Drops 0.05 % W/V 0.5 mg/ml, solution registered in the UK 1997. In the Netherlands, this product is registered by Meda Pharma B.V. through the MRP procedure (UK/H/255/001) under the name Allergodil. The marketing authorisation was granted in 1998.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. Azelastinehydrochloride Regiomedica differs from the reference product with regard to the absence of a preservative (benzalkoniumchloride, BAC) and the amount of sorbitol per ml. A single-dose presentation containing 0.3 ml of the solution is proposed. For this ocular formulation bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Azelastinehydrochloride Regiomedica is a clear, colourless to nearly colourless, slightly viscous solution with osmolality of 250– 320 mOsmol/kg and pH 5.5-6.5. Each ml contains 0.5 mg azelastine hydrochloride in a preservative free formulation. One drop contains 0.015 mg azelastine.

The solution is packed in 0.3 ml transparent LDPE single-dose containers in PET aluminium/PE sachets containing 5 single dose containers each.

The excipients are: liquid sorbitol (cristallizing) (E420), hypromellose (E464), disodium edetate (E386), sodium hydroxide (E524), purified water.

II.2 Drug Substance

The active substance azelastine hydrochloride is an established active substance, described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder, which is sparingly soluble in water, soluble in ethanol and in methylene chloride.
It has only one crystalline structure. The anhydrous form is manufactured, which is the most stable polymorphic form. It is the mixture of the R form and S form with one chiral centre.

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 flow chart and a short narrative description of the manufacturing process are provided. The starting materials, solvents and reagents are acceptable.

Quality control of drug substance
In addition to the requirements for azelastine hydrochloride described in the current monograph of the Ph.Eur., the following tests are performed: residual solvents and microbiological limits. Batch analysis data on three batches is provided. Sufficient information on reference standards or materials was given.

Stability of drug substance
In the stability studies no significant changes were observed, neither at long-term (25°C/60% RH, 36 months), nor at accelerated conditions (40°C/75% RH, 6 months). The stability studies will be continued. The retest period of the active substance is 3 years if stored in an well-closed container, protected from light.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. There is no incompatibility of the active substance with any of the excipients or with the package. The excipients used in the product are well known. Except for benzalkoniumchloride, the excipients of the product for registration are qualitatively the same as those of the innovator drug product. The sorbitol concentration is the same as in the Spanish reference product and is added to achieve the required osmolality. Therefore, limited differences can be accepted.
In-vitro data have been collected, comparing Azelastinehydrochloride Regiomedica 0.5 mg/ml eye drops with the originator products Allergodil Augentropfen, (Germany and Austria) and Corifina 0.5 mg/ml (Spain). Several parameters of the test and reference product were determined to investigate their similarity. Results are statistically evaluated. Parameters measured and compared are pH, relative density, osmolality, assay, sorbitol content, viscosity, droplet size and surface tension. These are considered as relevant parameters for determination of therapeutic equivalence. The results show that there are no relevant differences in pharmaceutical formulation between test and reference product.

Manufacturing process
The manufacturing process is a non-aseptic process of weighing and mixing. Subsequent filtration, filling and sealing of the containers are aseptic processes. Once the unit-dose container is moulded, the solution is filled. The manufacturing process includes in its final steps a sterilizing filtration. Process validation data on the product have been presented for three commercial scale batches. This is sufficient.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for identification, appearance, pH, relative density, osmolarity, viscosity, extractable volume, uniformity of dosage unit, integrity of the single-dose container and the sachet, assay, related substances and sterility. The release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches per presentation. The batch sizes correspond with commercial batch size and comply with the proposed specifications.

Stability of drug product
Stability data have been provided for three production-scale batches. These were stored at 25°C/40% RH for 24 months and 40°C/25%RH up to 6 months. The conditions used in the stability studies are in

accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in semi-permeable containers. All batches comply with the proposed set of specifications, at both temperatures tested. All tests remain within specifications up to 24 months. In-use stability data (temperature: 25ºC/40% RH) were collected for all three development batches at release and for one batch at the end of shelf-life. No significant change is seen.
Photostability of the drug product, as stated in ICH Q1B, is provided. The proposed shelf-life of 36 months is justified. The storage condition is 'Store in the original package' and 'Do not refrigerate or freeze". After first opening of the sachet, the shelf-life of the single dose containers is 28 days.

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 Azelastinehydrochloride Regiomedica 0.5 mg/ml, eye drops, solution, single dose container 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 Azelastinehydrochloride Regiomedica is intended for generic 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 generic formulation of Optilast, 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

Azelastine hydrochloride 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

Absorption of azelastine following ocular administration is relatively low, reaching a level of 0.02 to 0.25 ng/mL after 56 days of treatment.

Systemic absorption of azelastine after long-term administration of the eye drops may only lead to extremely low maximal plasma concentrations of azelastine. Adverse events related to systemic plasma levels of the compound are unlikely to occur.

IV.3 Clinical efficacy and safety

The efficacy of azelastine eye drops is well known. Sufficient literature data was made available.

The claim for essential similarity with the originator product is based on comparative quality attributes and literature to support the clinical irrelevance of the absence of BAC and other small differences. The MAH claims that the differences in some of the physical-chemical parameters, difference in sorbitol content and the absence of BAC have no significant influence on safety and efficacy of the product. Therefore the *in-vitro* comparison between test and reference product could be regarded as pivotal to demonstrate similarity of test and reference product.

The literature indicates that BAC might change the penetration of substances. This is relevant for products with intra-ocular mechanism of action. As this is not the case for azelastine, the absence of BAC is not considered as a hazard for the efficacy. Furthermore, a safety issue will also not arise since the penetration of azelastine, if any, will be less because of the absence of BAC.

The sorbitol concentration is the same as in the Spanish reference product and is added to achieve the required osmolality. Therefore, the small difference can be accepted. The differences in surface tension values, viscosity, pH and the osmolality are considered clinically irrelevant.
A pH between 6.5 and 8.5 is acceptable for eye drops. Therefore, the slight difference in pH between test and reference will not affect the tolerance, as the pH of the test product is closer to the reference limits compared to the originator. Furthermore, the pH of both test and reference products are not buffered.
The tolerance of the eye to administration of the eye drop will also not be affected by the difference in the osmolality because both test and reference product are very close to the physiological osmolality of the eye (290 – 310 mOsmol/kg). The higher sorbitol does not influence osmolality apparently.
The difference in density is marginal and within the variation in density of water due to changes in temperature between 20 and 37°C.
The surface tension values are within normal range. The viscosity of 1.1 – 1.5 indicates that the aqueous solution is hardly viscous. A slight difference is not considered to affect the retardation of presence of the eye drop on the eye surface.

Study nvc101012
A supportive clinical study was submitted to justify the absence of BAC in the product applied for. This was a phase III, two-armed, multi-centre observer-blind, randomized, clinical trial to evaluate the efficacy and safety of azelastine 0.5 mg/ml eye drops formulations with or without BAC in the relief of the seasonal or non seasonal allergic conjunctivitis. Two registered products were compared, i.e. Allergodil (registered in Germany and Austria, with BAC) and Corifina 0.5 mg/ml eye drops (in Spain, without BAC). This study was performed in order to demonstrate that efficacy and safety of azelastine ophthalmic solution are not influenced by the presence or absence of benzalkoniumchloride in the formula.

The study participants were 12 years of age or older, suffering of seasonal and non seasonal allergic conjunctivitis, not using topical ocular, inhaled or systemic steroids within 14 days prior to enrolment, or topical ocular, inhaled or systemic antihistaminic products within 7 days of enrolment.
Patients received the medication either the preservative-free or BAC containing formulation as one drop, 3 times a day (if needed, 5 times maximum) during 28 days.

This study was not conducted with the product applied for. The study was only intended to be supportive for establishing the effect of the absence of BAC on efficacy and safety. The study was considered insensitive to detect differences because assay sensitivity could not be demonstrated as the study lacks a placebo arm. As a consequence, the results can not be interpreted. A conclusion on non-inferiority is not possible. Besides the lack of assay sensitivity more obstacles were found in the design that could not be clarified. However, since essential similarity was sufficiently shown based on comparative quality attributes, a clinical study is not required.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, for Azelastinehydrochloride Regiomedica. The innovator of azelastine does not have an RMP. It is a known drug without any safety issues in the last several years. The summary of safety concerns can be accepted. No risks and no important missing information were identified. The member states agreed that routine pharmacovigilance activities are sufficient.

IV.5 Discussion on the clinical aspects

Based on the data provided, the test and reference product can be considered essentially similar. The literature showed sufficiently that no changes in efficacy are to be expected because of the absence of BAC. Since azelastine has its activity on the ocular surface i.e. at the conjunctivae, the absence of BAC is not considered as a hazard for the efficacy for azelastine. Furthermore, a safety issue will also not arise since the penetration of azelastine, if any, will be less because of the absence of BAC. No relevant differences in physical chemical parameters have been detected. The RMP is considered acceptable. This hybrid medicinal product can be used instead of the reference product.

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 participants tested were between 18 and over 65 years of age, with variable education level, male as well as female.
Diagnostic testing was performed. Questions (14 in total) were asked about all parts of the leaflet.
Two cohorts of 10 participants were interviewed. After the first round with 10 participants, no amendments of the PL were considered necessary. 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

Azelastinehydrochloride Regiomedica 0.5 mg/ml, eye drops, solution, single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Optilast Eye Drops 0.05 % W/V 0.5 mg/ml, solution. Optilast is a well-known medicinal product with an established favourable efficacy and safety profile.

Azelastinehydrochloride Regiomedica 0.05 mg/ml is a preservative free product for ocular use (eye drops) intended to act without systemic absorption. In contrast to the innovator product, it does not contain the preservative benzalkonium chloride. Chemical-physical properties are shown to be similar to the reference product, except for the surface tension. The MAH has provided sufficient documentation and argumentation to show that any observed difference is not considered clinically relevant. The test and innovator formulation may be considered equivalent with regard to efficacy and safety and therefore no clinical studies are required.

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 Azelastinehydrochloride Regiomedica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 March 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