LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Azelastine OmniVision
(azelastine hydrochloride)

SE/H/1183/01/DC

This module reflects the scientific discussion for the approval of Azelastine OmniVision. The procedure was finalised at 25 September 2013. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

OmniVision GmbH has applied for a marketing authorisation for Azelastine OmniVision, 0.5 mg/ml, eye drops, solution, as a hybrid application. The reference medicinal product is Azelastine 0.05%W/V Eye Drops authorised in the United Kingdom since 1998, with Meda Pharmaceuticals Limited as marketing authorisation holder.

The product contains azelastine hydrochloride as active substance. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Azelastine OmniVision is presented in the form of eye drops, solution containing 0.5 mg/ml of azelastine hydrochloride. The excipients are sorbitol liquid, hypromellose, disodium edetate, sodium hydroxide and purified water. The eye drops are filled in multidose dropper containers.

II.2 Drug Substance

Azelastine hydrochloride has a monograph in the Ph Eur.

Azelastine hydrochloride is a white or almost white, crystalline powder. It is slightly (*Ph Eur: sparingly*) soluble in water, soluble in ethanol and in methylene chloride. The structure of azelastine hydrochloride has been adequately proven. Relevant information on chirality is presented. The route of synthesis has been adequately described.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Azelastine OmniVision eye drops, solution is formulated using excipients described in the current Ph Eur. None of the excipients used in the manufacturing process is from human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

N/A

IV.2 Pharmacodynamics/Clinical efficacy/Clinical safety

While the originator contains benzalkonium chloride (BAK), Azelastine OmniVision does not. Besides that, Azelastine OmniVision contains the same excipients (qualitatively identical) as the originator, however, the concentration of sorbitol is somewhat higher compared to the originator.

The removal of BAK and the increased concentration of sorbitol may have an impact on the efficacy and safety, directly or as a change in physicochemical characteristics of the eye drop. Comparative in vitro studies indicate that physicochemical properties are sufficiently similar as the originator, however, a clinical study comparing the current product with Allergodil, the reference formulation approved in DE was performed.

The Study report presents the following outcome for the primary endpoint of the study:

Table 7: Responder distribution

Treatment group	Responder n (%)
Azelastine 0.5 mg/ml eye drops (N=75)	65 (86.7 %)
Allergodil™, Lab. Meda, Germany (N=75)	69 (92.0 %)

A total of 86.7 % of the patients treated with the test product (Azelastine 0.5 mg/ml eye drops without preservative) were responders with an at least 50% reduction in the eye symptom sum score of 87%. In the group treated with the reference product, in 92% of the patients the sum score for eye symptoms decreased of at least 50% compared to baseline. The 95% confidence interval for the difference in response rates has a distance from the difference to the CI limit of 9.8% (nQuery Advisor 7.0). Considering the non-inferiority margin of 10% Azelastine 0.5 mg/ml without preservative is not inferior to Allergodil™ 0.5 mg/ml with preservative.

For change in total symptom scores and for individual symptom scores (secondary endpoints), the study report presents data pointing to small differences between the two treatments. Summaries of mean changes and differences from baseline after 28 days treatment for the sumscore and for individual symptoms are given in the tables below.

Table Summary of change from baseline in total symptom score over time.

	Allergodil		**Azelastine 0.5 mg/ml eye drops**		**Difference (95% CI)**
	Mean	S.D.	Mean	S.D.	
Baseline	170.13	23.0	166.67	25.0	3.47 (-9.58, 16.51)
Day 7	-49.27	-65.3	-52.60	-62.9	3.33 (-7.19, 13.86)
Day 14	-97.27	-41.1	-100.5	-39.9	3.27 (-9.64 16.17)
Day 28	-136.0	-27.8	-133.5	-32.9	-2.53 (-15.76, 10.69)

Table Mean changes and differences from baseline after 28 days treatment for individual symptoms

	Allergodil	**Azelastine 0.5 mg/ml**	**Difference (95% CI)**
	Mean ± SD	Mean ± SD	
Tear production	-38.73 ± 15.73	-36.47 ± 18.69	-2.27 (-7.84, 3.31)
Ocular Itching	-51.20 ± 18.27	-51.67 ± 21.58	0.47 (-5.99, 6.92)
Ocular Redness	-46.07 ± 14.43	-45.33 ± 17.46	-0.73 (-5.90, 4.44)
Ocular Pain	-42.80 ± 14.66	-39.47 ± 17.98	-3.33 (-8.63, 1.96)
Ocular inflammation	-45.67 ± 14.60	-44.93 ± 17.85	-0.73 (-5.99, 4.53)

The study included 75 subjects per treatment arm and from a safety perspective such sample size would be too limited to discover any safety signals. However, since the concentration of sorbitol is increased compared to the originator and since no safety signals were reported in any of the treatment arms, the somewhat higher concentration of sorbitol in Azelastine eye drops appears not to raise any concerns.

IV.3 Discussion on the clinical aspects

In case of an eye drop where there are no changes in the composition compared to the originator, local absorption as well as local tolerance would expected to be similar between the two. Consequently, in such case, no impact on efficacy and safety would be expected and no clinical studies would be warranted.

BAK is generally used as a preservative, but, for some substances, also as solubiliser and, in occasional cases, to increase the transfer of certain compounds across the cornea, this since BAK increases the permeability of the corneal epithelium. Since azelastine is to act on the ocular surface, there should however be no concerns with regards to an impaired transfer into the eye that would be an issue for a compound with an intraocular mode of action.

The Applicant did however perform a clinical study. The study has a number of deficiencies that could be a concern if an intraocular action was targeted. Although the primary endpoint (Response rate, 50% reduction of the eye symptom sum score from baseline at the end of treatment - 28 days) may be considered acceptable, regarding mean change from baseline as the recommended primary endpoint according to NfG Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-conjunctivitis (CPMP/EWP/2455/02), no major differences were detected in mean differences from baseline for eye symptom sum score, the single eye symptoms (tear production, ocular itching, ocular redness ocular inflammation and ocular pain) as well as investigator cure score.

Further, in the statistical analysis plan (SAP), the symptoms included in the primary endpoint were not clearly defined (different number of variables on different places in the SAP) and the methods to evaluate the endpoints were not sufficiently detailed. Finally, the study was not

masked due to different appearances of the multidose bottle and the single dose units and a flexible dosing (according to the SPC section 4.2) was allowed.

Despite these deficiencies, in view of the lack of concern and this being a hybrid application and not a new product, the study is considered sufficient.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 language used for the purpose of user testing the PIL was Spanish.
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.

The risk/benefit ratio is considered positive and Azelastine OmniVision, 0.5 mg/ml, eye drops, solution, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Azelastine OmniVision, 0.5 mg/ml, eye drops, solution, was successfully finalised on 2013-09-25.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se