Public Assessment Report

Scientific discussion

VamocinMonafox
5 mg/ml eye drops, solution

Moxifloxacin hydrochloride

DK/H/2220/001/DC

This module reflects the scientific discussion for the approval of VamocinMonafox. The procedure was finalised at 21st November 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for VamocinMonafox 5 mg/ml eye drops, solution from Adamed Sp. z.o.o. The product is indicated in the treatment of purulent bacterial conjunctivitis, caused by moxifloxacin susceptible strains.

Moxifloxacin, a fluoroquinolon, is a synthetic broad-spectrum antibacterial agent, which has in vitro activity against a wide range of Gram-positive and Gram-negative pathogens.

Fluoroquinolones enter Gram-negative cells by two principle mechanisms. First, a porin-mediated mechanism that involves outer membrane proteins facilitates FQ transport into cells and leads to rapid accumulation. Second, fluoroquinolones chelation of membrane-associated magnesium enables the drug to enter the cell by lipopolysaccharide transport. Entry into Gram-positive cells is governed solely by fluoroquinolones hydrophobicity, the more hydrophobic the molecule the greater the intracellular accumulation. Some Gram-positive bacteria possess an energy-dependent efflux transport system that pumps the fluoroquinolones back out of the cell.

The bactericidal action of moxifloxacin results from the inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription and repair. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the norA or pmrA genes seen in certain Gram-positive bacteria.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Vigamox 5 mg/ml eye drops, solution marketed by Alcon Pharma GmbH.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each ml of eye drop, solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

The eye drops are a clear, greenish-yellow solution. with a pH between 6.3 and 7.3 and an osmolality of 290 mOsmol/Kg ± 5%.

The eye drops are provided in transparent-sterilized 10ml LDPE bottle, each containing 5ml. The LDPE bottle has LDPE dropper tip and HDPE tamper-proof screw-cap, consisting of a natural, low density polyethylene ophthalmic dispenser with a sealed dropper tip and a two-piece white –high density polyethylene closure cap assembly.

Excipients:
Sodium chloride
Boric acid
Sodium hydroxide
Water for injection

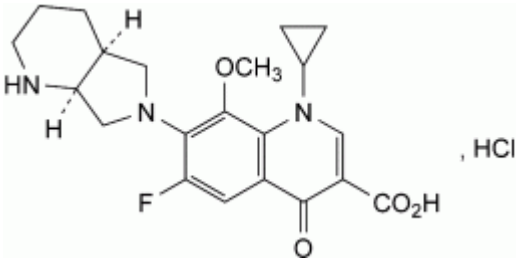
Compliance with Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The product contains the active substance moxifloxacin hydrochloride which is sourced from one supplier which is a holder of a Certificate of Suitability. The purchased active substance is a crystalline polymorphic form.

INN: Moxifloxacin hydrochloride



The active substance, Moxifloxacin, is described in the European Pharmacopoeia. Moxifloxacin is a light yellow powder or crystals, slightly hygroscopic, sparingly soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone.

The control tests and specifications for drug substance product are adequately drawn up. The provided stability data supports the proposed re-test period of 5 years.

II.3 Medicinal product

The finished product is an eye drops solution packaged in a transparent LDPE ophthalmic dispenser with a sealed dropper tip and a white HDPE closure cap, each containing 5 ml.

The development of the product has been described, the aim of which was to obtain a stable formulation matching the reference product with the same characteristics regarding pH, osmolality and specific gravity. The choice of excipients is justified and their functions explained. The excipients resemble those of the originator product and all are of Ph. Eur. quality.

The manufacturing process has in general been described sufficiently. The manufacturing process has been appropriately validated on production scale level and holding times are proposed based on evaluation of the bulk solution physicochemical stability. Bioburden and microbiological purity of the bulk solution stored need to be presented prior to approval of the proposed holding times. The Applicant is recommend to apply for the proposed holding times in a separate variation.

The product specifications cover appropriate parameters for this dosage form and satisfactory limits have been set for impurities complying with the ICH Q3B thresholds. Details and validations of all relevant analytical procedures are presented.

Batch analysis has been performed on 3 batches The batch analysis results show that the finished product meets the proposed specifications.

Stability studies have been conducted in accordance with ICH stability guidelines. No significant changes are observed for any of the investigated parameters and based on the presented data, covering 6 months at 40°C/75% RH, 18 months at 30°C/65% RH, 18 months at 30°C/75% RH and 24 months at 25°C/60% RH, there are no objections against the proposed shelf-life of 36 months (extrapolation by 12 months) with no special precautions for storage. The 4 weeks in-use shelf-life is also acceptable.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Vigamox 5 mg/ml eye drops, solution. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of moxifloxacin released into the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of moxifloxacin 5 mg/ml eye drops solution are well known. Moxifloxacin has been widely marketed and used and is well-established in medicinal use. It is broadly acknowledged to be efficacious and possessed of an acceptable risk benefit profile and on this basis, the applicant has not provided additional clinical studies and no further studies are required. An overview based on a literature review is therefore considered appropriate.

The applicant claims essential similarity between Moxifloxacin eye drops solution and the brand-leader Vigamox 5 mg/ml eye drops solution. Neither bioequivalence study nor clinical study of Moxifloxacin 5 mg/ml eye drops solution is presented to support the application on the basis that a biowaiver approach has been used. See further below.

A biowaiver is requested with reference to the Guideline "Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev. 1, Corr*). It is argued that as the product under consideration is a solution and has a similar excipient composition with that of the originator product Vigamox 5mg/ml eye drops solution, a waiver of the need to provide equivalence data is appropriate.

VamocinMonafox eye drops solution has been formulated to be essentially similar to Vigamox. A qualitative comparison of the compositions of both test and reference products has been presented.

Composition of VamocinMonafox 5 mg/ml eye drops, solution	Comparator product Vigamox 5 mg/ml eye drops, solution	Function
Moxifloxacin	Moxifloxacin	Drug substance
Boric Acid	Boric Acid	Antimicrobial preservative

NaOH 1N	NaOH or HCL (if necessary for pH-adjustment)	pH adjustment
Water for injection	Purified water	Diluent

An extensive in vitro investigation has also been performed on the physicochemical characteristics of both test and reference products, including specific gravity, pH, osmolality, average drop volume and surface tension. In addition, assay and related substance determinations have been performed and compared. The results support that there are no significant differences between test and reference product and that Moxifloxacin "Pharmathen" may be considered essentially similar to Vigamox.

IV.2 Risk management plan & Pharmacovigilance system

There is now more than 10 years post-authorisation experience with the active substance. The safety profile of moxifloxacine can be considered to be well established. No product specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The marketing authorisation holder has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Vigamox 5 mg/ml eye drops, solution.

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, 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

VamocinMonafox 5 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a generic form of Vigamox 5 mg/ml eye drops, solution. Moxifloxacin is a well-known active substance with an established favourable efficacy and safety profile.

An extensive in vitro investigation support that that there are no significant differences between test and reference product and that VamocinMonafox may be considered essentially similar to Vigamox.

The marketing authorisation holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and in agreement with other moxifloxacin containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for VamocinMonafox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 21st November 2013.