

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Ketotifen Eberth Unit Dose 0.25 mg/ml
eye drops, solution in single-dose container
Dr. Friedrich Eberth Arzneimittel GmbH, Germany**

ketotifen (as hydrogen fumarate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2430/001/DC
Registration number in the Netherlands: RVG 110580**

20 March 2013

Pharmacotherapeutic group:	ophthalmologicals, other antiallergics
ATC code:	S01GX08
Route of administration:	ocular use
Therapeutic indication:	symptomatic treatment of seasonal allergic conjunctivitis
Prescription status:	prescription only
Date of authorisation in NL:	27 November 2012
Concerned Member States:	Decentralised procedure with AT, DE, ES
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ketotifen Eberth Unit Dose 0.25 mg/ml eye drops, solution in single-dose container from Dr. Friedrich Eberth Arzneimittel GmbH. The date of authorisation was on 27 November 2012 in the Netherlands.

The product is indicated for symptomatic treatment of seasonal allergic conjunctivitis. A comprehensive description of the indications and posology is given in the SPC.

Ketotifen is a histamine H1-receptor antagonist. In vivo animal studies and in vitro studies suggest the additional activities of mast cell stabilisation and inhibition of infiltration, activation and degranulation of eosinophils.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zaditen ophtha sine 0.25 mg/ml, eye drops, solution in single-dose container marketed in Germany by Novartis Healthcare GmbH since 8 January 2001 (SE/H/0225/002/MR). In the Netherlands Zaditen Unidose 0.25 mg/ml is licensed (NL License RVG 25727) since 29 January 2001.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.

As Ketotifen Eberth Unit Dose 0.25 mg/ml eye drops, aqueous solution is a product for ocular use (eye drops) intended to act without systemic absorption, with qualitatively the same excipients used in the reference product, it is exempted for bioequivalence study (Guideline CPMP/239/95 on locally applied, locally acting products, containing known constituents).

No new pre-clinical and clinical studies were conducted (except for a tolerability study), which is acceptable for this generic application, because ketotifen hydrogen fumarate has been available already for a long time and the efficacy, pharmacology, pharmacokinetics and toxicology of the active substance are well-known.

No scientific advice has been given to the MAH with respect to this product and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB 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.

Active substance

The active substance is ketotifen hydrogen fumarate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to brownish-yellow, fine crystalline powder, which is sparingly soluble in water; slightly soluble in methanol and very slightly soluble in acetonitrile. No polymorphic form is observed in ketotifen fumarate.

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

Ketotifen fumarate is manufactured in five reaction steps. No class I organic solvents or heavy metal catalysts have been used. The manufacturing process is described in sufficient detail.

Quality control of drug substance

The drug substance specification of the MAH has been established in-house and is in line with the specifications of the DMF-holder. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance

Stability data on the active substance have been provided for five batches stored at 25°C/60% RH (60 months) and three batches stored at 40°C/75% RH (6 months). From the provided stability data no changes or trends are observed at both long-term and at accelerated conditions. The claimed retest period of 5 years is justified. No special storage conditions are required.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Ketotifen Eberth Unit Dose 0.25 mg/ml is a clear, colourless solution with pH 5.0-6.0 and osmolality of 230-300 mOsm/kg.

The eye drops are packed a transparent low-density polyethylene (LDPE) single-dose containers, sealed in aluminum laminated foil pouches. One single-dose container contains 0.4 ml. This 0.4 ml contains 0.138 mg ketotifen hydrogen fumarate corresponding to 0.1 mg ketotifen. Each drop contains approximately 9.6 microgram ketotifen hydrogen fumarate.

The excipients are: glycerol (E422), sodium hydroxide (E524) (for pH-adjustment), water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known and the same as in the reference product. The formulation does not contain any overages.

The qualitative composition in terms of the excipients and the quantitative composition in terms of the active substance are identical for the reference product and the proposed product. The MAH compared the surface tension between Ketotifen Eberth 0.25 mg/ml and the reference medicinal product. The submitted results show that the physicochemical properties are comparable with the reference product. Since the drug product is an ophthalmic product, the requirements for sterility are in compliance with Ph. Eur. 2.6.1. Sterility is achieved by aseptic processing and routine double sterile filtration. This is in accordance with the 'Note for Guidance on Development Pharmaceuticals' (CPMP/QWP/155/96) and the Annex 'Decision Tree for Selection of Sterilization Methods' (CPMP/QWP/054/98). Furthermore, the aseptic procedure is acceptable for this type of product.

The choices of the packaging and manufacturing process are justified.

Comparability of dosage

A dose reproducibility study has been performed with Ketotifen Eberth UD 0.25 mg/mL eye drops, solution.

The average drop size for one drop of Ketotifen Eberth UD 0.25 mg/mL eye drops, solution is 0.02796 mL (range 0.02712 – 0.0288 mL). For comparison, a drop size study was also performed for the reference medicinal product Zaditen® ophtha sine 0.25 mg/mL eye drops, solution, giving an average drop size of 0.02836 mL (range 0.02576 – 0.03096 mL).

Manufacturing process

The solution is manufactured by compounding, sterile filtration and aseptic filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the products have been presented for seven commercial scaled batches of 0.4 ml and 0.5 ml filled products. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients used comply with the requirements of the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, relative density, pH, osmolality, volume, water loss, assay, related substances and sterility. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two commercial-scale batches, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the product have been provided for seven pilot-scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the single dose container sealed in aluminium pouch.

Stability results showed that no significant changes or trends occur in the parameters tested. The drug product is not sensitive to light.

The proposed shelf-life of 2 years and storage condition "Do not store above 25°C" are justified. The conditions "Do not refrigerate or freeze" and "Keep the container in the aluminium pouch" are added.

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.2 Non-clinical aspects

This product is a generic formulation of Zaditen, which is available on the European market. 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.

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 ketotifen released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ketotifen 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.

Pharmacokinetics

For *oral* solutions no bioequivalence studies are necessary, however excipients which may affect absorption etc. should be taken into account. This is also applicable for this *aqueous eye drop solution*. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/05) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. This formulation is qualitatively identical to the reference medicinal product. Therefore a biowaiver is agreed.

Ketotifen Eberth Unit Dose 0.25 mg/ml eye drops, solution may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Clinical safety

A tolerability study has been conducted with Ketotifen 0.25 mg/ml eye drops, solution. Ocular tolerance of the test drug product was compared against physiological saline solution. The study was designed as a two-arm, randomized, controlled, double-blind, mono-centre phase I study. An intra-individual comparison was performed by comparing the tolerance of the ketotifen-containing eye drops, solution against the physiological saline solution (right against left eye).

Twenty-five healthy subjects, not suffering from any eye diseases and with no signs of swelling, redness and other findings in the eye, were recruited for this study conducted in Germany. No safety or tolerability concerns were identified in the study results.

Strictly speaking this study is not necessary as the same composition of Ketotifen Eberth 0.25 mg/ml compared to Zaditen Unidose 0.25 mg/ml eye drops allows bridging of the efficacy and safety from the innovator product to the generic. However, the results of the study support the tolerability of the eye drops solution.

Risk management plan

Ketotifen was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ketotifen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zaditen Unidose 0.25 mg/ml, eye drops, solution.

Readability test

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 two rounds with 10 participants each. A total of 14 specific questions were asked, all 14 covered the key messages for safe use of the product. In addition, 4 general questions were asked to gain an opinion/feedback of the subject's interpretation of the full package leaflet. 96.4% of the participants were able to find the information of whom 96.4% could show that they understood. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ketotifen Eberth Unit Dose 0.25 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Zaditen Unidose 0.25 mg/ml. Zaditen Unidose is a well-known medicinal product with an established favourable efficacy and safety profile.

Ketotifen Eberth Unit Dose 0.25 mg/ml is a product for ocular use (eye drops) intended to act without systemic absorption, with the same excipients used in the reference product, it is exempted for bioequivalence study.

The MAH demonstrated tolerability in a ocular tolerance test versus physiological saline solution. Surface tension between Ketotifen Eberth 0.25 mg/ml and the reference medicinal product were also shown to be comparable.

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

The SPC is based on that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Ketotifen Eberth Unit Dose 0.25 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 October 2012. Ketotifen Eberth Unit Dose 0.25 mg/ml eye drops, solution was authorised in the Netherlands on 27 November 2012.

The date for the first renewal will be: 4 October 2017.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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