COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ketotifen Stulln 0.25 mg/ml eye drops, solution in single-dose container

(ketotifen hydrogen fumarate)

NL/H/4462/001/DC

Date: 16 October 2019

This module reflects the scientific discussion for the approval of Ketotifen Stulln 0.25 mg/ml eye drops, solution in single-dose container. The procedure was finalised at 19 June 2019. 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
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 Ketotifen Stulln 0.25 mg/ml eye drops, solution in single-dose container, from Pharma Stulln GmbH.

The product is indicated for symptomatic treatment of seasonal allergic conjunctivitis.

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 Zaditen ophtha sine 0.25 mg/ml, eye drops, solution in single-dose container marketed in Germany by Laboratoires Théa S.A.S. 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 concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application. As Ketotifen Stulln 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.

II. QUALITY ASPECTS

II.1 Introduction

Ketotifen Stulln is a clear and colourless solution with a pH of 5.0-6.0 and an osmolality of 230-300 mOsm/kg. One ml solution contains 0.25 mg ketotifen (as hydrogen fumarate). Each single-dose container of 0.4 ml solution contains 0.1 mg ketotifen (as hydrogen fumarate). Each drop contains approximately 6.95 microgram ketotifen (as hydrogen fumarate).

The eye drops are packed in a transparent low-density polyethylene single-dose container. One single-dose container contains 0.4 ml. Either one, or two blocks of 5 single-dose containers each are packed in an aluminium laminated pouch.

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

II.2 Drug 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 and is sparingly soluble in water, slightly soluble in methanol and practically insoluble in heptane. No polymorphic form is observed in ketotifen fumarate.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH based on the specification of the Ph.Eur., an additional test for residual solvents, and a test for microbiological purity. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of drug substance.

Stability of drug substance
Stability data on the active substance have been provided as justification for the proposed retest period of 5 year without a storage condition.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference product and the comparative characteristics studies. The comparative studies included parameters pH, relative density, osmolality, impurities, assay, surface tension, viscosity and drop size. A waiver of the need to provide equivalence data can be considered in accordance with the Guideline on the Investigation of Bioequivalence, as the test product is the same type of aqueous solution and contains the same active substance and same excipients as the medicinal product currently approved. The excipients

used are well known and are the same as those present in the reference product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of preparing a bulk solution, filtration and aseptic filling and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. and additional microbiology requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour, identity, relative density, pH, osmolality, assay, related substances, filling volume, evaporative loss and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from nine batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for up to eleven batches at 25°C/60% RH (up to 36 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 an additive-free transparent low-density polyethylene single-dose container. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'Do not store above 25°C', 'Do not refrigerate or freeze' and 'Keep the container in the aluminium pouch'. When the aluminium pouch is opened the product remains stable for 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 Ketotifen Stulln 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)

An environmental risk assessment was provided and considered acceptable. However, since Ketotifen Stulln is intended for hybrid 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 Zaditen 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

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.

IV.2 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/EWP/239/95) 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 Stulln 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.

IV.3 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 Ketotifen Stulln.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Potential for off-label use (for other ophthalmic indications)
Missing information	- Use in children younger than 3 years of age - Use during pregnancy

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zaditen. No new clinical studies were conducted. Risk management is adequately addressed. 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 language used for the purpose of user testing the PL was German. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Ketotifen Stulln 0.25 mg/ml eye drops, solution in single-dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Zaditen ophtha sine 0.25 mg/ml, eye drops, solution in single-dose container. Zaditen ophtha sine is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

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 Stulln with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 June 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse