COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ketazed 0.25 mg/ml, eye drops, solution

(ketotifen hydrogen fumarate)

NL/H/4814/001/DC

Date: 10 March 2021

This module reflects the scientific discussion for the approval of Ketazed 0.25 mg/ml, eye drops, solution. The procedure was finalised at 12 November 2020. 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 for Ketazed 0.25 mg/ml, eye drops, solution, from Horus Pharma.

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 Unidose 0.25 mg/ml, eye drops, solution in single-dose container marketed in Netherlands by Laboratoires Théa since 29 January 2001 (NL License RVG 25727).

The concerned member states (CMS) involved in this procedure were Belgium, France, Luxembourg and Spain.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Ketazed is a clear and colourless solution with a pH of 4.8 – 6.4. One ml contains 0.345 mg ketotifen hydrogen fumarate corresponding to 0.25 mg ketotifen. Each drop contains 9.5 microgram ketotifen fumarate.

The eye drops solution is packed in a 10 ml white high density polyethylene bottle closed with a 3K® 28 µl dropper. One bottle contains 10 ml of sterile solution.

The excipients are: sodium hyaluronate, glycerol (E 422), sodium hydroxide (E 524) and purified water.

II.2 Drug Substance

The active substance is ketotifen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a fine crystalline powder and is sparingly soluble in water. No stereochemical or polymorphic issues are reported.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with an additional test for residual solvents as per CEP. Absence of a test for microbiological has been justified. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided which substantiate the proposed retest period of 5 year without a storage condition. Three batches were placed on stability at long-term conditions (30°C/75% RH) for up to 60 months and accelerated conditions (40°C/75% RH) for up to 6 months.

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 characterization of the reference product and comparative characteristics studies. The comparative studies included parameters pH, colour, density, osmolality, viscosity, buffering capacity, impurities, assay, extractable volume and drop mass. A waiver of the need to provide therapeutic equivalence data was requested by the MAH. This is acceptable even though there is a difference in qualitative composition with the reference product. The reference product Zaditen does not contain sodium hyaluronate. In line with NfG Clinical requirements for locally applied, locally acting products containing known constituents, if a different formulation is used in an abridged/hybrid application, clinical studies are in principle necessary to demonstrate safety/efficacy. However, the MAH has provided pharmaceutical data to justify that sodium hyaluronate does not impact the safety and the efficacy of the drug product . In addition, the test and reference product have similar pH and buffering capacity.

The pharmaceutical development of the product has been adequately performed. The acceptability for paediatric use has been discussed as per NfG on *Pharmaceutical development of medicines for paediatric use.*
The development of the 3K dropper system has been adequately explained and microbiological stress testing during the entire in-use period (7 days) has been performed.

Manufacturing process
The manufacturing process consists of preparing a bulk solution, filtration through a bacterial retentive filter and aseptic filling into pre-sterilised bottles. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 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, relative density, pH, filling volume, osmolality, water loss, identification, assay, related substances 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 three 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 three commercial scaled batches stored 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 the 3K container closure system. Photostability studies were not performed, which is acceptable in view of the white HDPE bottles. On basis of the data submitted, a shelf life was granted of 3 years for the unopened bottle when not stored above 25°C. Stability data have been provided demonstrating that the product remains stable for 7 days following first opening of the bottle.

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 Ketazed 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 Ketazed 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, pharmacodynamics, clinical efficacy and clinical safety

According to the applicant, Ketazed 0.25 mg/ml eye drops, solution has been developed as an ophthalmic generic (hybrid) formulation which has the same qualitative and quantitative composition in active substance with essentially similar physicochemical properties as the reference medicinal product (Zaditen 0.25 mg/mL, eye drops solution in single dose containers). Furthermore, the product presents the same pharmaceutical form as the reference medicinal product (eye drops solution). Considering the local administration route

and local activity of these ophthalmic products, bioequivalence cannot be demonstrated through bioavailability studies.

The MAH has performed viscosity studies to determine the rheological profile of the proposed formulation with sodium hyaluronate and has provided literature data to show that the presence of hyaluronate does not lead to a significant increase in absorption. Buffering capacity and pH have now shown to be comparable. With regard to the difference in drop size, the MAH has argued that the conjunctival sac can only contain up to 20 µl and the amount of ketotifen available in the eye would be similar between test and reference product based on similar density.

Overall, it has been concluded that similarity between test and reference products has been demonstrated.

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 Ketazed.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	- Use in 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 test consisted of a pilot test with 2 participants, followed by 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

Ketazed 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, eye drops, solution. Zaditen 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 Ketazed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 November 2020.

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