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Public Assessment Report

Name of the Product:

Ketotifen Bipharma

0.25 mg/ml single dose, eye-drops, solution

(ketotifen)

Procedure number: HU/H/0383/001/DC

Marketing authorisation holder: Bipharma B.V.

Date: 10 February 2016

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution. The holder of the marketing authorisation is Bipharma B.V.

The active substance is ketotifen (as ketotifen hydrogen fumarate). Each ml of solution contains 0.25 mg ketotifen (as 0.345 mg ketotifen hydrogen fumarate).

The other ingredients are glycerol, sodium hydroxide and water for injection.

Ketotifen Bipharma is presented as a clear solution, supplied in 0.4 ml clear plastic single-dose containers inside a sachet. There are five single-dose containers per sachet.

Ketotifen Bipharma is used to treat the eye symptoms of hay fever (seasonal allergic conjunctivitis). Hay fever is caused by an allergy to pollen and the symptoms are due to your immune system reacting to the pollen. Cells on the lining of your eyes release a chemical called histamine when in contact with pollen which causes your eyes to become red, itchy and watery. Ketotifen Bipharma relieves the eye symptoms of hay fever by blocking the action of histamine.

What patients need to know before using Ketotifen Bipharma

Those who are allergic to ketotifen hydrogen fumarate or any of the other ingredients of this medicine should not use Ketotifen Bipharma.

Other medicines and Ketotifen Bipharma

The doctor should be discussed, if the patient is using, have recently used or might use any other medicines. This is particularly important for medicines which are used to treat:
- depression,
- anxiety,
- difficulty sleeping,
- allergy (e.g. antihistamine).

If application of any other medicinal products to the eyes together with Ketotifen Bipharma is necessary, the patient should wait at least 5 minutes between applying each product.

Ketotifen Bipharma with food, drink and alcohol

Ketotifen Bipharma eye drops may increase the effect of alcohol.

Pregnancy and breast-feeding

Those who are pregnant, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Ketotifen Bipharma can be used during breast-feeding.

Driving and using machines

Ketotifen Bipharma may cause blurred vision or drowsiness. If this happens, the patient should wait until this has cleared before driving or operating machinery.

How to use Ketotifen Bipharma

The recommended dose for adults, elderly and children (age 3 and older) is one drop into the affected eye(s) twice a day (in the morning and evening).

One single-dose container contains enough solution to treat both eyes in one application.

Detailed instructions for use can be found in the package insert.

What happens if patients use more Ketotifen Bipharma they you?

If someone has accidentally used more eye drops than should, or has accidentally taken the eye drops by mouth, then this should not result in any harm. If having any doubt or questions, the doctor should be contacted for advice.

What happens if patients forget to use Ketotifen Bipharma?

If someone has forgotten to use Ketotifen Bipharma, he/she should treat the eyes as soon as it is remembered. Then it may be continued with the normal routine. However, patients should not take a double dose to make up for a forgotten dose.

Possible side effects

Like all medicines, Ketotifen Bipharma medicine can cause side effects, although not everybody experiences them.

The following side effects have been reported;

Common (that may affect up to 1 in 10 people) are:
- eye irritation or pain,
- inflammation in the eye.

Uncommon (that may affect up to 1 in 100 people) are:

- allergic reaction (including swelling of the face and eyelids) and increase in severity of existing allergic conditions such as asthma and eczema,
- blurred vision when putting drops on the eye,
- dry eye,
- eyelid disorder,
- conjunctivitis,
- increased sensitivity of the eyes to light,
- visible bleeding in white of eye,
- headache,
- drowsiness,
- rash (which may also itch),
- eczema (itchy, red, burning rash),
- dry mouth.

How to store Ketotifen Bipharma

Store it below 25ºC in the original package in order to protect from light.

Once the sachet is opened it must be used within 4 weeks. The contents of the single-dose container is to be used immediately after opening.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution. The procedure was finalised at 11 November 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use* an application has been submitted to the reference and competent authorities of the Member States concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Belgium and Netherlands) concerned a hybrid application. The product of this application is similar in composition to the approved product Zaditen 0.25 mg/ml colirio en solución envases unidosis Laboratories THEA, which has been authorized since 29 January 2001 in Spain. The two products have the same qualitative composition and their active ingredient is in the same concentration.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Ketotifen Bipharma 0.25 mg/ml eye drops, solution in single dose container from Bipharma B.V.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC. The product is of the same type of solution (aqueous) and contains the same concentration of the same active substance as the reference medicinal product Zaditen 0.25 mg/ml colirio en solución envases unidosis Laboratories THEA, Spain.

Ketotifen is indicated for the symptomatic treatment of seasonal allergic conjunctivitis.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics SmPC.

II. QUALITY ASPECTS

II.1 Introduction

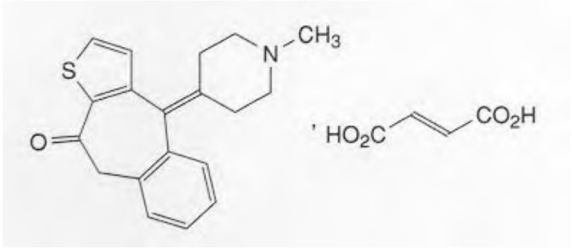
This chemical-pharmaceutical assessment report concerns the application Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution via a decentralized procedure according to Article 10 (3) of Directive 2001/83/EC (i.e. a hybrid application).

Reference product is Zaditen 0.25 mg/ml eye-drops, solution (containing 0.25 mg/ml ketotifen in the form of ketotifen fumarate as active ingredient) which was the original product of Laboratories THEA.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: ketotifen hydrogen fumarate
Chemical name: 4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10H-benzo[4,5]cyclohepta-[1,2-b]thiophen 10-one hydrogen (E)-butenedioate
Structure:



The active substance is white to brownish-yellow, fine, crystalline powder which is sparingly soluble in water, slightly soluble in methanol and very slightly soluble in acetonitrile.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents and microbiological purity.

The Ph. Eur. specification includes the following tests for ketotifen hydrogen fumarate: appearance, identification (by IR), appearance of solution, related substances, loss on drying, sulphated ash and assay of ketotifen hydrogen fumarate.

Testing methods are performed in accordance with the Ph. Eur. monograph and the annex of the current CEP on ketotifen hydrogen fumarate. The microbiological purity test was verified.

Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period has been justified by the submitted stability data. The applicant has justified the quality of the primary packaging material (inner colourless polyethylene bag and outer black polyethylene bag placed in fibre drum).

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to obtain an optimal formulation of ketotifen hydrogen fumarate in sterile solution for ophthalmic use with a suitable package to assure the quality, safety and efficacy. The qualitative and quantitative composition of the drug product is equivalent to the reference product, Zaditen 0.25 mg/ml eye drops, solution, the branded original product of Laboratories THEA.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards impurity profile and physico-chemical characteristics the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution is a clear solution containing 0.25 mg of ketotifen (base) as a drug substance per ml of solution.

The excipients used in the finished product are glycerol, sodium hydroxide and water for injections. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the product is 0.4 ml transparent low density polyethylene single-dose container. Each pre-formable PE aluminium/PET peelable sachet contains 5 single-dose containers. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 30 months unopened and 4 weeks after first opening of the sachet with the storage condition "Store below 25° C. Store in the original package in order to protect from light. Once the sachet is opened use within 4 weeks." is approved. (After opening the single-dose container: Use immediately after opening the single-dose containers.)

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ketotifen are well known, no further non-clinical studies are required in support of this hybrid marketing authorisation and therefore no new non-clinical data was provided in this application.

The applicant submitted a nonclinical overview based on a literature review of the pre-clinical pharmacology, pharmacokinetic and toxicology characteristics of ketotifen which is considered adequate. No further studies are required.

III.2 Pharmacology

The active substance in Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution is a relatively selective, non-competitive histamine antagonist (H_1-receptor) and mast cell stabilizer.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of ketotifen.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant. They do not deemed necessary for this type of application.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

The Ketotifen Bipharma 0.25 mg/ml single dose, eye-drops, solution is to be authorised via a hybrid procedure and it will be used interchangeably with other similar products already have been marketed in Europe. Thus, the introduction of this product onto the market is unlikely to result in any significant increase in the combined sales volumes for all ketotifen-containing ophthalmic products, and would thus not be expected to have an adverse effect upon the environment. For this reason a formal environmental risk assessment is not considered to be necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. Pharmacodynamics, pharmacokinetics and toxicology of ketotifen are well-known.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant has not submitted any new clinical studies and has stated this product essentially similar to the reference product based on pharmaceutical attributes. For topical products like eye drops that are deemed similar based on quality considerations, no clinical studies are required in line with Appendix II of the current EMA Guideline on the *Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), section on *Locally Acting Locally Applied Products*.

Ketotifen is a relatively selective, non-competitive histamine antagonist (H_1-receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from mast cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils have also been demonstrated. Ketotifen also inhibits cAMP phosphodiesterase. Properties of ketotifen which may contribute to its antiallergic activity and its ability to affect the underlying pathology of asthma include inhibition of the development of airway hyper-reactivity associated with activation of platelets by PAF (Platelet Activating Factor), inhibition of PAF-induced accumulation of eosinophils and platelets in the airways, and antagonism of bronchoconstriction due to leukotrienes. Ketotifen inhibits of the release of allergic mediators such as histamine, leukotrienes C4 and D4(SRS-A) and PAF.

IV.2 Pharmacokinetics

The application contains literature data.

As for absorption, in a pharmacokinetic study conducted in 18 healthy volunteers with ketotifen containing eye drops, plasma levels of ketotifen after repeated ocular administration for 14 days were in most cases below the limit of quantitation (20 pg/ml).

Elimination: the percentage of urinary excretion (9.8%) and the percentage of fecal excretion (83.3%) after ketotifen ocular instillation has been reported to be similar to those obtained after oral or intravenous administration.

After oral administration, ketotifen is eliminated biphasically, with an initial half-life of 3 to 5 hours and a terminal half-life of 21 hours. About 1% of the substance is excreted unchanged in the urine within 48 hours and 60 to 70% as metabolites. The main metabolite is a practically inactive ketotifen-N-glucuronide.

IV.3 Pharmacodynamics

The clinical pharmacology of ketotifen is well known. No novel pharmacodynamic data have been supplied or required for this application.

Ketotifen is a histamine H_1-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.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this type of application. The applicant has provided an adequate literature review to describe the efficacy profile of ketotifen.

IV.5 Clinical safety

No new safety data have been submitted and none are required for this type of application. The applicant has provided an adequate literature review to describe the safety profile of ketotifen.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of its Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• none
Important potential risks	• off-label use
Missing information	• use during pregnancy

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage the safety concerns related to ketotifen 0.25mg/ml single dose eye drops solution product of Bipharma B.V. No additional activities are proposed.

Risk minimisation measures: in general, routine risk minimisation measures (i.e. wording in SmPC, PIL and classification as a prescription only medicine) are considered sufficient to manage the safety concerns related to ketotifen 0.25mg/ml single dose eye drops solution product of Bipharma B.V. No additional activities are proposed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

The application concerns a hybrid submission of a product under Article 10(3) of Directive 2001/83/EC as amended, referring to Zaditen 0.25 mg/ml colirio en solución envases unidosis Laboratories THEA, which has been authorized since 29 January 2001 in Spain.

The submitted product is of the same type of solution (aqueous) and contains the same concentration of the same active substance as the reference medicinal product.

The method and means of administration of the test product is the same as that of the reference medicinal product.

The indication is the symptomatic treatment of seasonal allergic conjunctivitis.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution. The holder of the marketing authorisation is Bipharma B.V.

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

The application was submitted according to Article 10(3) of Directive 2001/83/EC (hybrid application). The reference product was Zaditen 0.25 mg/ml colirio en solución envases unidosis Laboratories THEA.

The application contains an adequate review of published clinical data and similarity with the reference product based on pharmaceutical attributes has been proven. The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the member states have granted marketing authorisation for Ketotifen Bipharma 0.25 mg/ml single dose, eye drops, solution.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 patient information leaflet was Hungarian.

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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached