COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bradexa 3 mg/ml + 1 mg/ml eye drops, suspension

(tobramycin/dexamethasone)

NL License RVG: 123316

Date: 10 March 2020

This module reflects the scientific discussion for the approval of Bradexa 3 mg/ml + 1 mg/ml eye drops, suspension. The procedure was finalised on 2 September 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Bradexa 3 mg/ml + 1 mg/ml eye drops, suspension, from Rockmed Pharma B.V.

The product is indicated for prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

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

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Tobradex 3 mg/ml + 1 mg/ml eye drops, suspension (NL RVG 14223) which has been registered in The Netherlands by Novartis Pharma B.V. since 26 April 1991.

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

II. QUALITY ASPECTS

II.1 Introduction

Bradexa is a white suspension with a pH between 5.0 and 6.0. Each ml of eye drops suspension contains 1 mg dexamethasone and 3 mg tobramycin.

The suspension is in LDPE dropper bottle with a HDPE/LDPE screw cap with a capacity of 10 ml. Only 5 ml of suspension is filled.

The excipients are: benzalkonium chloride, edetate disodium, sodium chloride, sodium sulfate (anhydrate), tyloxapol, hydroxyethyl cellulose (may contain phosphate buffers), sulfuric acid and/or sodium hydroxide (for pH adjustment) and water for injection.

II.2 Drug Substances

The active substances are tobramycin and dexamethasone, established active substances described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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 European Pharmacopoeia.

Tobramycin

Tobramycin is a white or almost white powder. The active substance is very soluble in water, freely soluble in formamide, slightly soluble in methanol and practically soluble in ethanol. Tobramycin has the potential of forming polymorphs and a mixed crystal form is used.

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 is in line with the Ph.Eur. and CEP and also contains an additional test for microbial count. The identification tests are the second identification tests as approved by EDQM. Several analytical procedures are not according to Ph.Eur. and additional information regarding suitability and equivalence has been shown. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for twenty-two full-scaled batches stored at 25 °C/60% RH (up to 60 months) and accelerated conditions of 40 °C/75% RH (up to 6 months). A re-test period of 60 months can be granted.

Dexamethasone

Dexamethasone is a white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in anhydrous ethanol and slightly soluble in methylene chloride. The active substance shows polymorphism and form B is consistently manufactured.

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 with the Ph.Eur. and the CEP with additional requirements for particle size and microbial count. The analytical procedures are not all according to the Ph.Eur. or CEP but information regarding suitability and equivalence to Ph.Eur. methods has been provided. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for thirteen industrial scaled batches stored at 25 °C/60% RH (60 months) and accelerated conditions of 40 °C/75% RH (6 months). The re-test period of 2 years as claimed by the MAH can be granted in view of the re-test period stated on the CEP (5 years).

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 development studies were focussed on the manufacturing process including sterilisation. The composition of the product is aligned with the innovator product, based on patent information. A waiver for clinical studies is requested and essential similarity is based on physical-chemical comparison (pharmaceutical equivalence). The relevant parameters (appearance, pH, osmolality, particle size, drop size, viscosity, surface tension and impurities) have been compared and data of three batches of Tobradex and three batches of test product have been provided. The results are similar/within range of the innovator product and hence equivalence has been shown. The pharmaceutical development of the product has been adequately performed including preservative efficacy testing. The MAH has shown that the lowest level as included in the shelf-life specification is suitable for preservative efficacy according to Ph.Eur.

Manufacturing process

The manufacturing process consists of twelve steps and has been validated according to relevant European guidelines. Process validation data on the product have been presented for eight full-scaled batches in accordance with the relevant European guidelines. Additional validation reports have been provided regarding media fill, filtration studies (filter challenge, filter integrity, leachables), sterilisation of the empty packaging materials. ISO statements of the sterilisation sites are provided.

Control of excipients

The excipients comply with the Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes

The drug product is routinely tested for sterility. This is in line with the requirements for eye drops solutions of the general Ph.Eur. eye preparations monograph.

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, pH, osmolality, uniformity of volume, assay, identification, related substances, particle size, sterility and water loss. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The limits are identical for release and shelf-life except for assay of active substances and preservative, impurities of dexamethasone and osmolality. A test for

uniformity of drop size is not added, which is acceptable in view of the control strategy of the dropper. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from eight full-scaled 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 from eight full-scaled batches stored at 25 °C/75% RH (up to 24 months) and 40 °C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The shelf-life period of 24 months with no specific storage conditions can be granted. Although the solution itself is susceptible to light degradation, the product in the bottle is sufficiently protected. A storage restriction regarding protection from light is not considered necessary as the liquid will not be stored outside the bottle. An in-use period of 4 weeks has been substantiated by data. The MAH has adopted a warning regarding refraining from refrigeration and freezing.

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 MEB considers that Bradexa 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 Bradexa 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 Tobradex 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 MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tobramycin and dexamethasone are well-known active substances 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative attributes of the product. 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. Since the qualitative and quantitative composition of both products is similar to that of the reference products Tobradex 3 mg/ml + 1 mg/ml eye drops, suspension and the pharmaceutical properties (i.e. osmolarity, pH, relative density and droplet volume) are comparable to that of the reference product as well, a biowaiver can be granted. Bradexa 3 mg/ml + 1 mg/ml eye drops, suspension may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal 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 Bradexa.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tobradex. 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 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 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

Bradexa 3 mg/ml + 1 mg/ml eye drops, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Tobradex 3 mg/ml + 1 mg/ml eye drops, suspension. Tobradex 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.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Bradexa was authorised in the Netherlands on 2 September 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