COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Triamcinolonacetonide ACE 1 mg/ml, acid ear drops

(triamcinolone acetonide)

NL License RVG: 126609

Date: 4 September 2023

This module reflects the scientific discussion for the approval of Triamcinolonacetonide ACE 1 mg/ml, acid ear drops. The procedure was finalised on 21 December 2022. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety, and efficacy data, the MEB has granted a marketing authorisation for Triamcinolonacetonide ACE 1 mg/ml, acid ear drops, from ACE Pharmaceuticals B.V.

The product is indicated in the treatment of wet acute otitis externa with severe itching in adults and children.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the product is applied locally and a bioequivalence study cannot be performed.

In this national procedure, essential similarity is proven between the new product and the innovator product Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g (NL RVG 33246) which has been registered in the Netherlands by Tiofarma B.V. since 9 September 2010.

II. QUALITY ASPECTS

II.1 Introduction

Triamcinolonacetonide ACE is a clear and colourless solution. The solution has a pH of 2.0 - 4.0, 10 ml of acid ear drops contains 10 mg triamcinolone acetonide.

The excipients are: acetic acid, propylene glycol (E1520) and water.

The solution is packed in brown glass bottles with a clear glass dropper fitted with a screw cap and a balloon.

II.2 Drug Substance

The active substance is triamcinolone acetonide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is practically insoluble in water. The drug substance exhibits polymorphism, but the polymorphic form has not been identified as the drug product is a solution.

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. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for two scaled batches.

Stability of drug substance
Assessment of the stability of the drug substance was part of granting the CEP (and has been granted by the EDQM).

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 purpose of the development was to obtain an identical formulation of the reference product Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g. The formulation is designed to deliver a good therapeutic product for the treatment of acute otitis externa. Overall, the pharmaceutical development has adequately been performed.

Manufacturing process
The manufacturing process consists of mixing the ingredients and filling the solution in bottles. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

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

Microbiological attributes
The microbiological quality is controlled according to Ph. Eur. 5.1.4. The sterility of the product is considered to be adequately controlled.

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, identification of triamcinolone acetonide, assay of triamcinolone acetonide, related substances, identification of acetic acid, assay of acetic acid and microbiological quality. The release and shelf-life limits are identical for all tests, except for related substances, and are acceptable. Limits in the

specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two commercial 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 for two commercial scaled batches stored at 25°C/60% RH (6 months) and 2-8°C (12 months). The stability was tested in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 12 months when stored at 2-8°C. The photostability of the drug product has been adequately addressed. The in-use stability studies, performed with two batches near the end of shelf-life, support an in-use shelf-life of four weeks.

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 Triamcinolonacetonide ACE 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 Triamcinolonacetonide ACE is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Triamcinolone acetonide 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 MEB agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The medicinal product is a locally applied locally acting non-sterile solution for ear drops. Considering the local administration route and local activity of this otic product, bioequivalence cannot be demonstrated through bioavailability studies. Essential similarity is based on comparative and physiochemical attributes of the product.

The composition of the product is considered identical to the reference product (Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g) concerning pH, viscosity, and relative density. Additionally, the fill volume of the two products is identical. Therefore, it can be accepted that only the drop volume has been taken into account. The difference in drop volume has been compared between the test and reference product and the difference is smaller than 15%, which is acceptable.

Therefore, a biowaiver can be granted. Triamcinolonacetonide ACE may be considered as therapeutic equivalent, with the same efficacy and 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 Triamcinolonacetonide ACE.

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

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB 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 Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zure oordruppels met Triamcinolonacetonide DMB 0.1% FNA. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Triamcinolonacetonide ACE 1 mg/ml, acid ear drops has a proven chemical-pharmaceutical quality and is a hybrid form of Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA, ear drops, solution 1 mg/g. Zure oordruppels met triamcinolonacetonide DMB 0,1% FNA is a well-known medicinal product with an established favourable efficacy and safety profile.

As Triamcinolonacetonide ACE 1 mg/ml, acid ear drops is a product for auricular use (ear drops) intended to act without systemic absorption, with a comparable composition to the reference product, it is exempted for bioequivalence study and therapeutic equivalence is considered established.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Triamcinolonacetonide ACE with the reference product, and have therefore granted a marketing authorisation.

The national procedure was finalised with a positive outcome on 21 December 2022.

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
-	-	-	-	-	-