COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hydrocortison 1% ACE, acidic eardrops (hydrocortisone)

NL License RVG: 126374

Date: 21 October 2021

This module reflects the scientific discussion for the approval of Hydrocortison ACE. The marketing authorisation was granted on 23 April 2021. 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
FNA	Formularium der Nederlandse Apothekers
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 Hydrocortison 1% ACE, acidic eardrops from ACE Pharmaceuticals B.V.

The product is indicated for wet infection of the external ear canal (otitis externa), accompanied by severe itching. 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 acidic eardrops with Hydrocortison DMB 1% FNA, (NL RVG 33245) which has been registered in the Netherlands by TioFarma B.V. since 9 September 2010 (original product).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Hydrocortison 1% ACE is a clear colourless solution and contains as active substance 10 mg of hydrocortisone per ml of solution.

The solution is packed in a brown, glass bottle of 10 ml with a clear glass dropper and is equipped with a screw cap and balloon. The bottle with dropper is packaged in a box.

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

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

II.2 Drug Substance

The active substance is hydrocortisone, an established active substance described in the European Pharmacopoeia. 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 European Pharmacopoeia.

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 in line with the Ph. Eur. requirements, with additional requirements from the CEP for particle size, atomic absorption and residual solvents plus microbiological quality. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance

The retest period of the drug substance is not covered by the CEP. Stability data on the micronized active substance in long-term (25 °C/60% RH) and at 30 °C/65% RH conditions have been provided for 17 batches. Based on the results, a shelf-life of 36 months is acceptable. The batches were stored in a polyethylene bag or double polyethylene bags placed in a metal can or fibre drum. A re-test period was granted for 36 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.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of mixing the ingredients and filling the solution in bottles. The manufacturing process validation data are acceptable. Process validation data on the product have been presented for two commercial-scale 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.

Quality control of drug product

The product specification includes tests for appearance, pH, identification of hydrocortisone, assay of hydrocortisone, identification of acetic acid, assay of acetic acid, related substances and microbiological quality. The release and shelf-life limits are identical, except for assay and related substances. Batch analytical data from the proposed production site have been provided on two commercial-scale batches demonstrating compliance with the release specification. A risk evaluation on nitrosamine impurities has been provided.

Stability of drug product

Stability results up to 15 months in long-term (2-8 °C) and six months in accelerated (25 °C/60% RH) have been provided. Significant changes in assay and related substances were observed in accelerated conditions, but not in long-term conditions. The photostability of the drug product has been adequately addressed. A shelf-life of 12 months is claimed when the product is stored at 2-8 °C and is considered acceptable. In-use stability studies have been performed, which support the in-use shelf-life of one month.

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 Hydrocortison 1% 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 Hydrocortison 1% ACE, acidic eardrops is a hybrid product, it 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

Pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well known. As hydrocortisone is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on a non-clinical overview is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydrocortisone 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 agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

The medicinal product Hydrocortison 1% ACE, acidic eardrops is administered as an otic solution. There are no specific pharmacokinetic data on this product. Because the intended administration route is a topical one, the hydrocortisone is metabolized locally in the skin. Only if it is applied for an extended period of time on a large area does it have systemic absorption. In this particular product the systemic absorption is negligible.

Biowaiver

As the composition of Hydrocortison 1% ACE, acidic eardrops is the same as that of the reference product, acidic eardrops with Hydrocortison DMB 1% FNA (TioFarma), a bioequivalence study is not required. Therefore, a waiver of bioequivalence can be granted if in vitro comparison of physicochemical parameters of the test and reference product are provided.

The formulation aspects of Hydrocortison 1% ACE, acidic eardrops have been demonstrated to be suitable by the reference product acidic eardrops with Hydrocortison DMB 1% FNA and are in line with Formularium der Nederlandse Apothekers (FNA) monograph acidic eardrops 1%, November 2019 (in FNA since 1995). The manufacturer has produced the product conform specifications provided by FNA, so the composition of the proposed product is considered identical to the reference product concerning pH, viscosity and relative density. Also the fill volume of the two products is identical. Assay and level of related substances present are highly dependent on the age of the product investigated. As a matching age between proposed and reference product cannot be established, results of analysis will differ inherently. Therefore, chemical comparison of proposed and reference product is considered indecisive in establishing bioequivalence. The decisive factor in bioequivalence is the dose applied, as this is dependent on the dropper supplied. A comparison in drop weight between one batch of proposed product and one batch of reference product has been performed. Only one batch of reference product was tested due to recent short supply of reference product. As there was no significant difference in the most decisive quality attribute on bioequivalence, bioequivalence between proposed and reference product is considered demonstrated. Therefore, a biowaiver of bio equivalence studies can be considered to be acceptable.

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 Hydrocortison 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 acidic eardrops with Hydrocortison DMB 1% FNA. No new clinical studies were conducted. The MAH demonstrated through a drop volume comparison study that the product is similar to the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

No consultation with the target patient group is needed as Hydrocortison 1% ACE 10 mg/ml, acidic eardrops is a generic product based on the reference medicinal product acidic eardrops with Hydrocortison DMB 1% FNA. This is a generic medicine, not a new active substance and has not undergone a change in legal status. It does not need a new presentation and there are no critical safety issues. The package leaflet is based on the reference medicinal product acidic eardrops with Hydrocortison DMB 1% FNA. The layout and the language of both the Hydrocortison 1% ACE 10 mg/ml, acidic eardrops and the acidic eardrops with Hydrocortison DMB 1% FNA package leaflets is identical. The following three points concerning Hydrocortison 1% ACE 10 mg/ml, acidic eardrops are identical to the reference medicinal product; key messages for safe use, the design and layout issues and the complexity of message and language used. Seeing as the Hydrocortison 1% ACE 10 mg/ml, acidic eardrops package leaflet is identical to the package leaflet of acidic eardrops with Hydrocortison DMB 1% FNA, it was concluded that no readability test needs to be conducted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Hydrocortison 1% ACE 10 mg/ml, acidic eardrops has a proven chemical-pharmaceutical quality and is a generic form of acidic eardrops with Hydrocortison DMB 1% FNA. Hydrocortison DMB is a well-known medicinal product with an established favourable efficacy and safety profile

No bioequivalence has been shown to be in compliance with the requirements of European guidance documents. As Hydrocortison 1% ACE, acidic eardrops is administered as an otic

solution, there are no specific pharmacokinetic data on this product. Because the intended administration route is a topical one, the hydrocortisone is metabolized locally in the skin. Only if it is applied for an extended period of time on a large area does it have systemic absorption. In this particular product the systemic absorption is negligible. The MAH submitted a comparison in drop weight between one batch of proposed product and one batch of reference product instead. As the decisive factor in bioequivalence is the dose applied, and this being dependent on the dropper supplied, this is considered acceptable. Therefore the lack of bioequivalence studies is justified.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). However, a written opinion procedure was started after the second assessment round. The issues discussed involved the tightening of the shelf-life to nine months, the tightening of the shelf-life limit for assay and the unacceptability of the in-use stability protocol. These issues were resolved by the MAH after additional information was provided. The information that was provided included stability data at 2-8 ℃ up to 15 months where no significant changes or out-of-specification results were observed. A shelf-life of 12 months is claimed and can be granted, based on the additional data. Furthermore, the tightened shelf-life limit for assay of hydrocortisone was accepted in view of the additional stability data and type of drug product. Finally, in-use stability results were provided by the MAH, which support an in-use shelf-life of one month. An agreement that all issues are considered to be resolved and that the product can be registered was reached.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hydrocortison 1% ACE with the reference product, and have therefore granted a marketing authorisation. Hydrocortison 1% ACE was authorised in the Netherlands on 23 April 2021.

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