COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fusidinezuur Basic Pharma 20 mg/g cream

(fusidic acid)

NL/H/4344/001/MR

Date: 13 October 2020

This module reflects the scientific discussion for the approval of Fusidinezuur Basic Pharma 20 mg/g cream. The procedure was finalised at 3 December 2018. 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 Fusidinezuur Basic Pharma 20 mg/g cream, from Basic Pharma Manufacturing B.V.

The product is indicated for the topical treatment of non-severe, superficial, non-extensive, skin infections caused by microorganisms that are sensitive to fuaidic acid, especially of infections caused by *Staphylococcus* in adults and children. Skin infections that may be expected to respond to treatment with fusidic acid applied topically include: impetigo contagiosa, impetiginized dermatosis, superficial folliculitis, sycosis barbae, paronychia and erythrasma.

Official (local) guidance regarding the correct use of antibacterial agents should be considered.

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

This mutual recognition procedure concerns a hybrid application claiming essential similarity with the innovator product Fucidin 20 mg/g Cream which has been registered in Denmark by Leo Pharma AS since 4 May 1962 (original product). In the Netherlands, the reference product is Fucidin crème 20 mg/g, cream, which has been registered since 2 December 1981 via a national procedure.

Fusidinezuur Basic Pharma 20 mg/g cream has obtained the marketing authorisation via duplicate registration in the Netherlands. This application was initially submitted using the decentralised procedure with the United Kingdom as reference member state (RMS) and Belgium, Germany, Luxembourg, the Netherlands and Poland as concerned member states (CMS). The Netherlands has been requested to acts as new RMS for this product. This mutual recognition application for Fusidinezuur Basic Pharma is used to add Germany and Spain as new CMS.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application. As required by article 10(3) a comparative clinical trial needs to be performed to demonstrate therapeutic equivalence, as showing bioequivalence by pharmacokinetics is not possible.

II. QUALITY ASPECTS

II.1 Introduction

Fusidinezuur Basic Pharma is a white, homogenous cream. Each gram contains 20 mg fusidic acid.

The cream is packed in aluminium tubes with a HDPE screw cap.

The excipients are butylhydroxyanisole (E 320), cetyl alcohol, glycerol 85% (E422), liquid paraffin, potassium sorbate (E 202), polysorbate 60 (E435), white soft paraffin, hydrochloric acid (for pH adjustment) and purified water.

II.2 Drug Substance

The active substance is fusidic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fusidic acid is a white or almost white crystalline powder and practically insoluble in water and freely soluble in alcohol.

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.

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 objective of the development programme was to produce a safe, efficacious, product that was comparable in performance to the originator product, Fucidin.

Manufacturing process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. Test methods have been described and adequately validated, as appropriate.

Batch data have been provided and comply with the release specification. Certificated of Analysis have been provided for any working standards used.

Stability of drug product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed for the unopened tube and four weeks for the opened tube, with the storage conditions “Do not store above 25°C.”

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 Fusidinezuur Basic Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fusidinezuur Basic Pharma 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 Fucidin 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

The clinical pharmacology of fusidic acid is well-known. With the exception of the below therapeutic equivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

IV.2 Clinical efficacy

The MAH provided a multicentre, randomised, 2-arm, double-blind parallel, comparative clinical trial to compare the efficacy and safety of the test product Fusidic acid 20 mg/g cream (Basic Pharma Manufacturing BV, The Netherlands) in adults and children greater than 18 months with a clinical diagnosis of localised impetigo contagiosa.

Subjects were randomised to one of the two treatments. The dose of cream applied (to fully disinfected lesions) was dependent on the location of the lesions and the age of the patient. Treatment was followed for a maximum period of 14 days, or until the lesions disappeared. The primary endpoint was rate of "cure" at one week. "Cure" was defined as the complete absence of lesions or the lesions having become dry and without crusts; remaining local erythema of the intact skin is acceptable, or such progress that no further antibiotic therapy was necessary. Non-inferiority was assumed if the 95% CI were within a pre-specified 20% limit.

The results for primary endpoint are presented below:

Table 1. Clinical efficacy of the intended to treat population after 1 week.

Clinical efficacy parameter	Fusidic acid 20 mg/g (test) N=85	Fucidin 20 mg/g (reference) N=87	Total N=172
Cured	55 (64.7%)	54 (62.1%)	109 (63.4%)

The difference is 2.6% in favour of Fusidic acid 20 mg/g cream with a 95% confidence interval of -11.6 to 16.7%.

Usually for this type of product a more stringent non-inferiority margin of 10% is applied. However the MAH had provided suitable justification for the proposed 20% non-inferiority margin. Hence non-inferiority of the proposed product in comparison to Fucidin 20 mg/g cream (Leo Pharma BV, The Netherlands) has been established.

As the reference product used in the therapeutic equivalence study is considered identical to the reference product in the United Kingdom, therapeutic equivalence has also been shown between the proposed product Fusidic acid 20 mg/g cream (Basic Pharma Manufacturing

BV) and the United Kingdom reference product Fucidin Cream (Leo Laboratories Limited, The United Kingdom).

IV.3 Clinical safety

With the exception of the data generated during the therapeutic equivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the therapeutic equivalence study data.

IV.4 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 Fusidinezuur Basic Pharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	– Hypersensitivity
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Fucidin. No new clinical studies were conducted. The MAH demonstrated through a therapeutic equivalence study that the efficacy and safety profile of the product is similar to the efficacy and safety profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fusidinezuur Basic Pharma 20 mg/g cream has a proven chemical-pharmaceutical quality and is a hybrid form of Fucidin 20 mg/g Cream. Fucidin is a well-known medicinal product with an established favourable efficacy and safety profile.

Non-inferiority of this product in comparison to Fucidin has been established, with no statistically/clinically significance differences observed between products.

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 Fusidinezuur Basic Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised/mutual recognition procedure was finalised with a positive outcome on 3 December 2018.

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