IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fusidic acid/Betamethasone Galenpharma 20+1mg/gram(s) Cream
Fusidic acid
Betamethasone valerate
PA23425/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fusidic acid/Betamethasone Galenpharma 20 mg/g + 1 mg/g cream, from GALENpharma GmbH on 24th June 2024 for use in inflammatory eczema ordermatoses where bacterial infection is present or likely to occur. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This application concerns a decentralised procedure according to Article 28(3) of Directive 2001/83/EC with Ireland as the Reference Member State and Germany as the only Concerned Member State. The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC [A so-called "hybrid application"].

The European product referred to in the application is Fucibet 20 mg/g + 1 mg/g cream authorised in Ireland since 23rd May 1984 (PA0046/040/001). It has been authorised in the EEA in accordance with Union provisions for not less than 6/8/10 years.

This product is subject to medical prescription which may not be renewed.

Scientific Advice was given on two occasions by the MHRA (UK). This Scientific Advice pre-dated the departure of the UK from the European Union and the development of the relevant draft Guideline on Quality and Equivalence of Topical Products (CHMP/QWP/708282/2018). However, this Scientific Advice appears to have been followed by the applicant.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Fusidic acid/Betamethasone Galenpharma 20+1mg/gram(s) Cream
Name(s) of the active substance(s) (INN)	Fusidic acid/Betamethasone valerate
Pharmacotherapeutic classification (ATC code)	D07CC01
Pharmaceutical form and strength(s)	20+1mg/gram(s) Cream
Marketing Authorisation Number(s) in Ireland (PA)	PA23245/001/001
Marketing Authorisation Holder	GALENpharma GmbH
MRP/DCP No.	IE/H/1228/001/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fusidic acid/Betamethasone Galenpharma 20+1mg/gram(s) Cream.

II.2 Drug substance

The active substances are fusidic acid and bethamethasone, established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications have been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

Certificates of suitability issued by EDQM have been provided and compliance with the Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

Adventitious viruses

N/A

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Fusidic acid/Betamethasone Galenpharma 20+1mg/gram(s) Cream.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the Irish market for 40 years. Preclinical data have been superseded by clinical experience and therefore no pre-clinical assessment has been made on the application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Fusidic acid/Betamethasone Galenpharma 20mg/g + 1mg/g Cream is a hybrid formulation considered essentially similar to the reference product Fucibet 20 mg/1mg cream, an increase in environmental exposure to the active substances is not anticipated, which has been substantiated by suitable data (consumption data for the last 4 years). Additional studies on environmental risk are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Fusidic acid and betamethasone valerate are widely used and well-known active substances. The reference product Fucibet, contains the same active substances in the same concentrations. The pharmacodynamic, pharmacokinetic and toxicological properties of the active substances are well-understood and well-described in the literature. No new nonclinical studies are presented in this submission; an overview based on literature review was provided and is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fusidic acid and betamethasone valerate are well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Fucibet 20 mg/g + 1 mg/g cream.

Overall, comprehensive data has been provided in support of therapeutic equivalence. The following studies have been deemed satisfactory by the RMS:

- Physico-chemical comparison of between test and reference products.
- In vitro release study between test and reference products
- In vitro human skin permeation study to compare skin penetration/permeation between test and reference product.
- In vitro/ex vivo study in infected human skin to compare microbiological activity of fusidic acid between test and reference products**.**
- In vivo skin blanching study for betamethasone valerate between test and references product.

In addition to the above studies, an in vitro release study at shelf-life (i.e. after 24 months' storage) is also presented in the dossier.

Based on the data package provided, it can be concluded that the proposed product is therapeutically equivalent to the European Reference Product.

IV.2 Pharmacokinetics

In vitro and in vivo skin penetration studies demonstrated rapid penetration of both fusidic acid and betamethasone valerate through the epidermis into the subcutaneous tissue, and that fusidic acid penetrates at a rate similar to corticosteroids.

Damage and other disease processes in the skin are likely to affect the level of percutaneous absorption of both active compounds.

IV.3 Pharmacodynamics

In their Clinical Overview the applicant states that it is recognised in the 'Note for guidance on the clinical requirements for locally applied locally acting products containing known constituents' (CPMP/EWP/239/95 final) that it is generally not possible to demonstrate clinical equivalence between two topically applied products via conventional pharmacokinetic bioequivalence studies. In some instances, it is possible to employ pharmacodynamic equivalence studies in lieu of clinical efficacy studies, an example being for topical steroids using the well-recognised 'skin blanching' assessment. Such a study has been included in the application. With the majority of drug substances, however, there is no recognised pharmacodynamic model that can be used to infer clinical equivalence, this indeed is the case with the fusidic acid component of the application product.

IV.4 Clinical Efficacy

The applicant has provided a brief clinical overview of atopic dermatitis and its pharmacological management The applicant has also provided a review of published literature of the efficacy profile of fusidic acid and betamethasone valerate relating to the proposed indication. No company efficacy studies have been submitted and this is acceptable in keeping with the legal basis of this application.

IV.5 Clinical Safety

The applicant has provided a review of published literature relating to bacterial resistance and local tolerance. No company safety studies have been submitted and this is acceptable in keeping with the legal basis of this application.
Contraindications are clearly outlined in the product information to ensure the correct target patient population, and to ensure correct use. For example, there is an absolute contraindication in paediatric patients aged less than two years due to the betamethasone valerate content, which is considered a highly potent steroid and in line with the reference product in CMS Germany and recently approved DCPs with these actives. The Product Information clearly outlines to healthcare professionals and patients which infections and skin conditions this product is not suitable for, advice against long-term use is included to avoid the risk of systemic absorption of steroids, adverse local effects and the development of bacterial resistance. Clinical trial and post-marketing experience indicate that any anticipated side effects are either uncommon or rare. No differences in the safety profile between adult and paediatric patients are apparent.

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 Fusidic acid/Betamethasone Galenpharma 20mg/g + 1mg/g Cream.

Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

If the data requirements of Article 10(3) of Directive 2001/83/EC are met, efficacy and safety studies are generally not required for such products. The RMS is satisfied that the Article 10(3) data requirements have been met and therapeutic equivalence to the European reference Product has been shown. The indication in the SmPC and PIL has been aligned with that of the Reference Product, otherwise the wording proposed in the product information is thought to enhance the benefit-risk balance of the proposed generic product. The SmPC highlights that "consideration should be given to official guidance on the appropriate use of antibacterial agents". This statement is intended to reduce the risks of bacterial resistance due to inappropriate or over-use of antimicrobials such as fusidic acid.

V. OVERALL CONCLUSIONS

Fusidic acid/Betamethasone Galenpharma 20 mg/g + 1 mg/g cream is a generic form of Fucibet 20 mg/g + 1 mg/g cream. Fucibet 20 mg/g + 1 mg/g cream is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The SmPC is overall consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, based on the data submitted considered that Fusidic acid/Betamethasone Galenpharma 20 mg/g + 1 mg/g cream, from GALENpharma GmbH
demonstrated equivalence with the reference product as well as a satisfactory risk/benefit profile and is therefore granted a marketing authorisation.

VI. REVISION DATE

24.06.2029