Public Assessment Report

Scientific discussion

Fusidinsyre/betamethasonvalerat "Leo"
20 mg/g + 1 mg/g cream

(Fusidic acid and betamethasone (as valerate))

DK/H/2355/001/DC

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This module reflects the scientific discussion for the approval of Fusidinsyre/betamethasonvalerat "Leo". The procedure was finalised on 19 January 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fusidinsyre/betamethasonvalerat "Leo" 20 mg/g + 1 mg/g cream, from LEO Pharma A/S.

The product is indicated for: Infected atopic dermatitis and dermatitis, especially allergic and toxic eczema infected by microorganisms sensitive to fusidic acid.
A comprehensive description of the indications and posology is given in the SmPC.

Eczemas may often be infected with pathogenic microorganisms, especially Staphylococcus aureus, with the clinical need of application of a combination-corticosteroid, such as fusidic acid/betamethasone, possessing both anti-microbial and anti-inflammatory properties.

This decentralised procedure concerns a hybrid application against the reference product Fucicort 20 mg/g + 1 mg/g cream which has been registered in Denmark by LEO Pharma A/S since 1986.
Fusidinsyre/betamethasonvalerat "Leo" cream is a reformulation of the long-established Fucicort cream, in a different vehicle with higher lipid content. Both products contain the same active components fusidic acid and betamethasone in the same concentrations. Fucicort cream has been in extensive clinical use since 1986 and Fucicort Lipid cream was approved in Denmark as an extension to Fucicort cream in 2006. Fucicort Lipid cream was a useful addition because of the lipidrich formulation that is more suited to certain dry skin types in AD.

The marketing authorisation is granted based on article 10.3 of Directive 2001/83/EC.

The product is pharmaceutically equivalent (same quantitative and qualitative composition and same manufacturing method) to Fucicort Lipid cream.

II. QUALITY ASPECTS

II.1 Introduction

The cream contains fusidic acid 20 mg/g and betamethasone as betamethasone valerate 1 mg/g.

It is a white cream packed in aluminium tubes with polyethylene screw caps in tube sizes of 5 g, 15 g, 30 g and 60 g. However, not all tube sizes may be marketed.

The cream contains: Steareth-21; Cetostearyl alcohol; White soft paraffin; Liquid paraffin; Hypromellose; Citric acid monohydrate; Methylparahydroxy benzoate (E 218); Propylparahydroxy benzoate (E 216); Potassium sorbate; All-*rac*-α-tocopherol and Water, purified.

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The finished product contains two active substances, micronised fusidic acid and micronised betamethasone valerate.

Fusidic acid
Fusidic acid is a white or almost white microcrystalline powder. It is freely soluble in alcohol, insoluble in water and insoluble in the chosen oil-in-water formulation. The lacking aqueous solubility is a matter of high melting point, about 192°C, and a very lipophilic nature with a low Kow of 6.75. Fusidic acid is sensitive to light and prone to oxidation.

The manufacturer of the active substance has obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The active substance is controlled according to the requirements of the Ph. Eur. monograph with additional requirements.

The control tests and specification for the active substance has been adequately set. The re-test period is according to the CEP. The Ph. Eur. monograph for fusidic acid includes the following text concerning storage: "Protected from light, at a temperature of 2-8°C".

Betamethasone valerate
Betamethasone valerate is a white or almost white microcrystalline powder, insoluble in water, soluble in alcohol and insoluble in the chosen oil-in-water formulation. Melting at about 192°C with decomposition. Betamethasone valerate is a lipophilic substance with a log Kow of 3.94. Betamethasone valerate is sensitive to light and prone to oxidation.

The manufacturer of the active substance has obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The active substance is controlled according to the requirements of the current Ph. Eur. monograph.

The control tests and specification for the active substance has been adequately set. The CEP does not include a re-test period. Stability data for micronised betamethasone valerate has been presented, and an appropriate re-test period has been set.

II.3 Medicinal Product

The product applied for in this decentralised procedure is already approved nationally in Denmark under the tradename Fucicort Lipid, LEO Pharma A/S. In addition a less lipid rich formulation of the product is approved nationally in Denmark under the trade name Fucicort, LEO Pharma A/S. Thus, it is acknowledged that the Applicant has extensive insight and knowledge of the proposed finished product. Therefore, it is to some extent acceptable to draw parallels between the product nationally approved and the proposed product.

Each active substance is suspended as micronised material in the cream. The choice and the functions of the excipients have been adequately justified. The development of the product has been described.

The dosage form and the manufacturing process are considered standard cf. EU "Guideline on process validation for finished products – information and data to be provided in regulatory submission" EMA/CHMP/CVMP/BWP/70728/2012-Rev1). Satisfactory process validation has been conducted with three batches of each of the proposed lower batch sizes. Confirmation has been given that process validation also will be performed on batches of the largest batch size when manufactured, protocol to be followed has been presented in section 3.2.R.

The product specifications cover appropriate parameters for this dosage form. Validation of the analytical methods has been conducted and data presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished product meets the specifications proposed.
Stability reports have been presented. The storage conditions are in accordance with EU/ICH stability guideline (with exemption of a few older batches). The finished product has been demonstrated unstable at accelerated conditions (40°C/75%RH), hence stability testing at intermediate conditions

(30°C/75%RH) have been conducted in addition to the long-term stability testing. The presented stability data justifies a shelf-life period of 2 years with the storage condition "do not store above 30°C". An in-use shelf-life period of 3 months has been demonstrated.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of fusidic acid and betamethasone valerate are well known. As fusidic acid and betamethasone valerate is a widely used, well-known combination product, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 88 publications up to year 2013. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

In addition to literature references, studies performed in support of marketing authorisation of different formulations of fusidic acid and betamethason were mostly performed prior to the ICH guidance documents on GLP, and follow the current practice prior to establishing these. Therefore few (if any) studies are in concordance with GLP regulations. This is considered acceptable, as the clinical experience with combination preparations of fusidic acid and betamethason is extensive.

In the non-clinical overview submitted, a brief overview of the resistance mechanisms towards fusidic acid is presented. The Applicant sufficiently justifies that although resistance mechanisms have been identified, as the overall resistance towards fusidic acid is relatively low, and fusidic acid is therefore considered to be of therapeutic value, as there appears to be less potential to resistance development compared to alternative topical products. The corticosteroid component of Fusidinsyre/betamethasonvalerat "Leo" is betamethasone valerate, which has been established as having accentuated anti-inflammatory properties, while remaining corticosteroid properties are depressed.

Permeation of fusidic acid and betamethasone valerate in the Fucicort Lipid cream formulation was studied in intact and abraded pig skin, and it was established that the permeation of betamethasone valerate and fusidic acid was 3- and 4- fold greater (respectively) than from Fucicort cream formulation. In 2011, a clinical study assessing the pharmacokinetics and safety of fusidic acid doses of up to 1650 mg was performed, where no clinically significant differences in laboratory or ECG parameters were observed.

III.2 Ecotoxicity/environmental risk assessment (ERA)

An environmental risk assessment of fusidic acid and betamethasone valerate has been submitted.

The partition coefficient (n-octanol/water) for fusidic acid is sensitive to pH. A log Kow value of 2.7 at pH 7.5 indicates that the potential for bioaccumulation in the environment with the actual pH conditions is very low and fusidic acid cannot be expected to accumulate significantly in organisms or sediment.

A log Kow value of 3.6 for betamethasone valerate indicates a risk of bioaccumulation in the environment according to the EU Guidance document.
However, as log KOW at pH about 7 for both of the drug substances are less than 4.5, a screening for persistence, bioaccumulation and toxicity are not performed.

It was established that at the expected use of Fusidinsyre/betamethasonvalerat "Leo" cream, the predicted environmental concentration (PEC surfacewater) would be below the limit of 0.01 µg/L, no Tier II assessment is required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The present application for Fusidinsyre/betamethasonvalerat "Leo" is based on Article 10(3) of Directive 2001/83/EC.

The qualitative and quantitative composition of Fusidinsyre/betamethasonvalerat "Leo" is the same as for Fucicort Lipid cream authorised in Denmark.

Fusidinsyre/betamethasonvalerat "Leo" is pharmaceutically equivalent (same quantitative and qualitative composition and same manufacturing method) to Fucicort Lipid cream. Thus, the proposed product is considered bioequivalent to the reference product according to the Guideline of Investigation of Bioequivalence as they are pharmaceutically equivalent and their bioavailability is univocally the same. This justifies that bioequivalence documentation is not part of the present application as experimental studies are not required.

Because the generic product is biopharmaceutically equivalent to the reference product as stated above, the safety and efficacy profiles are also the same.

IV.2 Clinical efficacy

The evaluation of safety and efficacy of Fucicort Lipid cream was based on one major study comparing Fucicort Lipid cream to Fucicort cream and lipid cream vehicle and six supportive studies comparing Fucicort cream to topical antibiotic/betamethasone 17-valerate or in one study betamethasone 17-valerate alone. The populations in the studies analysed for safety and efficacy were well matched and corresponds to the proposed targeted group and is consistent with the inclusion criteria applied in the clinical studies analysed.

The major study comparing Fucicort Lipid cream to Fucicort cream and lipid cream vehicle included 629 patients. In this study the clinical and antibacterial cream was found to be similar to that of Fucicort cream in patients with eczema and significantly better than that of the Lipid cream vehicle. No significant differences in the incidence of adverse events were found between the Fucicort Lipid cream and Fucicort cream or Lipid cream vehicle.

The clinical efficacy and safety profile of Fucicort cream is well known. In the six supportive studies, Fucicort cream was compared with betamethasone 17-valerate alone and other betamethasone 17-valerate/antibiotic combinations. In these studies, Fucicort cream was found to be marginally better or similar in clinical efficacy compared to the active comparators. Fucicort cream also demonstrated similar or better bacteriological efficacy to the betamethasone 17-valerate antibiotic comparators.

IV.3 Clinical safety

No significant differences in the incidence of adverse events were found between the Fucicort Lipid cream and Fucicort cream or Lipid cream vehicle in the pivotal study.

The clinical efficacy and safety profile of Fucicort cream is well known. In the six supportive studies, Fucicort cream was compared with betamethasone 17-valerate alone and other betamethasone 17-valerate/antibiotic combinations. In these studies, Fucicort cream was found to be marginally better or similar in clinical efficacy compared to the active comparators. Fucicort cream also demonstrated similar or better bacteriological efficacy to the betamethasone 17-valerate antibiotic comparators. The safety of Fucicort cream was similar to the control products used in the published studies analysed.

Many years of clinical use have shown a favourable safety profile, with only few and mild side effects, in the treatment of infected eczema with Fucicort cream and Fucicort Lipid cream.

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 Fusidinsyre/betamethasonvalerat "Leo".

The following summary list of safety concerns has been agreed with no additional pharmacovigilance or risk minimisation measures:

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

Summary of safety concerns	
Important identified risks	• Hypothalamic-pituitary-adrenal axis suppression • Masking, activation or aggravation of skin infection • Allergic reactions • Corticosteroid induced dermal atrophy • Allergic contact dermatitis
Important potential risks	• Teratogenic effects
Missing information	• Use during pregnancy

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 language used for the purpose of user testing the PIL was English.
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.

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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fusidinsyre/betamethasonvalerat "Leo" 20 mg/g + 1 mg/g cream has a proven chemical-pharmaceutical quality and is identical to Fucicort Lipid, LEO Pharma A/S. Fucicort Lipid is a well-known medicinal product with an established favourable efficacy and safety profile.

Fusidinsyre/betamethasonvalerat "Leo" is considered bioequivalent to the reference product according to the Guideline of Investigation of Bioequivalence as they are pharmaceutically equivalent and their bioavailability is univocally the same.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. A Risk Management Plan has been presented summarising the safety concerns.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fusidinsyre/betamethasonvalerat "Leo" 20 mg/g + 1 mg/g cream with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 19 January 2015. Fusidinsyre/betamethasonvalerat "Leo" 20 mg/g + 1 mg/g cream was authorised in Denmark on 25 March 2015.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), the next DLP is 1 January 2021, after which the PSUR cycle is 9 years.

The date for the first renewal will be: 19 January 2020.

The following post-approval commitments have been made during the procedure:

- The MAH accepts to undertake work in order to demonstrate the suitability of the analytical procedure AP-00120 in terms of specificity regarding impurities.

- The MAH accepts to undertake work in order to demonstrate the suitability of the analytical procedure AP-00330 in terms of specificity regarding impurities.