Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Betafuse 1 mg/g + 5 mg/g gel for dogs [AT, BE, CY, EE, DE, EL, IT, IE, LV, LT, MT, NL, PT, ES, UK]

Betafuse Vet 1 mg/g + 5 mg/g gel for dogs [FI, SE]
Betafuse Vet [DK]

Date Created: September 2016

PuAR correct as of 28/11/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0577/001/DC
Name, strength and pharmaceutical form	Betafuse 1 mg/g + 5 mg/g Gel for Dogs
Applicant	Norbrook Laboratories Limited Station Works, Camlough Road Newry County Down Northern Ireland BT35 6JP
Active substance(s)	Betamethasone (as betamethasone valerate) 1 mg Fusidic acid (as fusidic acid hemihydrate) 5 mg
ATC Vetcode	QD07CC01
Target species	Dogs
Indication for use	For the treatment of acute surface pyoderma in the dog, such as acute moist dermatitis (‘hot spots’) and intertrigo (skin fold dermatitis), caused by Gram-positive bacteria sensitive to fusidic acid.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	29th June 2016.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Portugal, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended as 'hybrid' applications. The reference product is Trigoderm Gel 0.5% w/w Fusidic acid, 0.1% Betamethasone marketed in the UK since March 1995. The application was submitted under Article 13 (3) because bioavailability between the proposed product and the reference product cannot be demonstrated for this topically applied and acting product via relevant clinical studies. The product was deemed to be identical to the reference product by way of essential similarity with regard to pharmaceutical form, strength, and qualitative and quantitative composition.

The product is indicated for the treatment of acute surface pyoderma in the dog, such as acute moist dermatitis ('hot spots') and intertrigo (skin fold dermatitis), caused by Gram-positive bacteria sensitive to fusidic acid. The product is for cutaneous use. A 0.5 cm length of product per 8 cm^2 of lesion should be applied twice daily for a maximum of five days.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 1 mg/g betamethasone (as betamethasone valerate), 5 mg/g fusidic acid (as fusidic acid hemihydrate) and the excipients sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate, carbomer, polysorbate 80, dimethicone, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and purified water.

The container/closure system consists of a white polyethylene coated aluminium tube of 15 g or 30 g closed with a polypropylene cap. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence of preservative are justified.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the placement of water in a manufacturing vessel, addition of sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate. Subsequent addition of the excipients is followed by mixing and cooling, determination of pH of the gel and filling into packaging.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are fusidic acid and betamethasone valerate (micronised), established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. All excipients are described in the Ph. Eur, the container-closure for the product is described in a certificate of suitability.

II.C.4. Substances of Biological Origin

A declaration of compliance with the *Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*, EMEA/410/01 Rev. 2, has been provided by the applicant together with a Format 3 form stating that all materials are of non-animal origin. Additionally, it has been declared by the active substance providers that no materials of mammalian origin are present during the manufacture of the substances.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, content and identification of active substances, particle size, viscosity, uniformity of dosage units, fill weight, pH and microbial quality.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The retest period for fusidic acid is 30 months when the product is suitably stored at 2°C – 8°C in polyethylene bags in drums. A retest period of 5 years was agreed for betamethasone valerate when suitably stored in polyethylene bags in drums.

Stability studies were performed on the finished product in line with VICH[3] guidelines, and suitable 'in-use' data were provided.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

Shelf life after first opening the container: 8 weeks.

[3] VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

This veterinary medicinal product does not require any special storage conditions.

III.A Safety Documentation

The products are generic hybrid applications, and as such no additional pharmacological or toxicological data are required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Published LD_{50} values were quoted for the active substances:

- People with known hypersensitivity to the active ingredients or to any of the excipients should avoid contact with the veterinary medicinal product.
- Corticosteroids may produce irreversible effects in the skin; they can be absorbed and may have harmful effects, especially with frequent and extensive contact or in pregnancy. Pregnant women should take special care to avoid accidental exposure.
- Always wear single-use impermeable gloves when applying this product to animals.
- Wash hands after having applied the product.
- Care should be taken to avoid contact with treated areas of the animal, for the duration of the treatment period.
- Care should be taken to avoid accidental ingestion by a child. In the case of accidental ingestion, seek medical advice immediately and show the package leaflet to the physician.

Environmental Safety

As the product is not intended for use in animals for human consumption and will only be used in individual animals, a Phase I environmental risk assessment was sufficient. Appropriate warnings appear on the SPC and product literature.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, no pre-clinical studies were required.

Tolerance in the Target Species

Due to the nature of the application, no tolerance data were required.

Resistance

A literature review was provided. In order to update the data relevant to the reference product, the SPC for the proposed product was revised to include more recent data. Adequate warnings and precautions appear on SPC and product literature:

- Two major mechanisms of resistance to fusidic acid hemihydrate have been reported in *S. aureus* – the alteration of the drug target site which is due to chromosomal mutations in FusA (encoding elongation factor EF-G) or FusE encoding ribosome protein L6, and the protection of the drug target site by FusB family proteins, including fusB, fusC, and fusD. The fusB determinant originally was found on the plasmid in *S. aureus* but has also been found on a transposon-like element or in a staphylococcal pathogenicity island.

- No cross-resistance between fusidic acid hemihydrate and other antibiotics that are in clinical use has been identified.

IV.II. Clinical Documentation

Laboratory Trials

In relation to the type of application, the applicant provided bibliographical data and a clinical field trial to support non-inferiority between the proposed and reference products. With regard to essential similarity as provided for under the guideline EMA/CVMP/016/00-Rev.2, and in the interests of scientific pragmatism, although the guideline was not written for topically applied products, the proposed product is considered essentially similar to the reference product. No further data were required.

Field Trials

The field trial provided was not pivotal to the approval of the marketing authorisation because essential similarity was confirmed between the proposed and reference products. No further data were required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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