Public Assessment Report

Decentralised Procedure

Fusidic Acid 2% Cream

UK/H/5525/001/DC

PL 00289/1849

Teva UK Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Fusidic Acid 2% Cream. It explains how Fusidic Acid 2% Cream was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Fusidic Acid 2% Cream.

For practical information about using Fusidic Acid 2% Cream patients should read the package leaflet or contact their doctor or pharmacist.

What is Fusidic Acid 2% Cream and what is it used for?
Fusidic Acid 2% Cream is a hybrid generic medicine. This means that it contains the same active substance (fusidic acid) in the same dose as the reference product Fucidin 20mg/g cream.

Fusidic Acid 2% Cream is used for the treatment of skin infections caused by bacteria that are sensitive to fusidic acid (especially staphylococcus infections) such as impetigo (a weeping, crusty and swollen patch of skin), folliculitis (inflammation of one or more hair follicles), sycosis barbae (infection of the bearded skin), paronychia (infection of the tissue surrounding a fingernail or toenail) and erythrasma (infection with brown, scaly skin patches, especially in the folds of the body). It is also used to treat infected dermatitis (inflammation of the skin), spots, cuts and grazes.

How is Fusidic Acid 2% Cream used?
Usually a small amount of cream is gently applied to the infected skin three or four times each day. A sterile bandage or dressing may be recommended by a doctor, which can usually reduce the number of applications needed.

The duration of the treatment will be decided by a doctor. Treatment usually lasts 1 to 2 weeks, although it may be longer depending on the type of infection and the result of the treatment. If the cream is used for a long time or in large amounts then there is a higher chance of getting side effects.

Fusidic Acid 2% Cream can only be obtained with a prescription.

How does Fusidic Acid 2% Cream work?
Fusidic acid is an antibiotic (this means that it kills bacteria that cause infections).

Fusidic acid prevents bacteria from producing the proteins that they need to multiply. Fusidic acid does not directly kill the bacteria, but leaves them unable to increase in numbers. The remaining bacteria eventually die or are destroyed by the immune system. This treats the infection.

How has Fusidic Acid 2% Cream been studied?
A clinical study was conducted to investigate whether Fusidic Acid 2% Cream is as effective as the reference product Fucidin 20mg/g cream in treating adults and children with impetigo.

What benefit has Fusidic Acid 2% Cream shown during studies?
In the study patients treated with Fusidic Acid 2% Cream had a cure rate that was comparable to the cure rate for patients treated with Fucidin 20mg/g cream.

What is the risk associated with Fusidic Acid 2% Cream?
For the full list of all side effects reported with Fusidic Acid 2% Cream, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why is Fusidic Acid 2% Cream approved?
It was considered that the benefits of using Fusidic Acid 2% Cream to treat skin infections caused by sensitive bacteria outweigh the risks and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Fusidic Acid 2% Cream?
A Risk Management Plan has been developed to ensure Fusidic Acid 2% Cream is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fusidic Acid 2% Cream, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Fusidic Acid 2% Cream
The MHRA agreed to grant a Marketing Authorisation for Fusidic Acid 2% Cream on 16 October 2014.

For more information about treatment with Fusidic Acid 2% Cream, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2014.

The full PAR for Fusidic Acid 2% Cream follows this summary.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Fusidic Acid 2% Cream could be approved. This prescription only medicine (POM) is used for the treatment of non-severe, superficial, non-extensive, primary and secondary skin infections caused by microorganisms that are sensitive to fusidic acid, especially infections caused by Staphylococcus.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium and Germany as Concerned Member States (CMS). This application was made under Article 10(3) of Directive 2001/83/EC, as amended, as a so-called hybrid generic application. The reference medicinal product for this application is Fucidin 20mg/g cream, which was first authorised to Leo Pharma AS in Denmark on 4 May 1962. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

Fusidic acid belongs to a unique group of antibiotics, the fusidanes, which act to inhibit bacterial protein synthesis by blocking the lengthening of factor G. This is to prevent it from associating with ribosomes and GTP, thus preventing energy supply to the synthesis process.

A clinical study comparing the proposed product to the reference product in patients with impetigo was submitted with the application. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

No new non-clinical data were submitted, which is acceptable given that the application is for a product which is a hybrid generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

Since Fusidic Acid 2% Cream is intended for generic substitution, its use will not lead

to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

The RMS and CMS considered that the application could be approved at Day 210 of the procedure on 25 September 2014. After a subsequent national phase, the Marketing Authorisation was granted in the UK on 16 October 2014.

II Quality aspects

II.1 Introduction

The product is a white, homogenous cream. Each gram contains 20 mg fusidic acid. The excipients are butylhydroxyanisol (E 320), cetyl alcohol, glycerol (85%), liquid paraffin, potassium sorbate (E 202), polysorbate 60, white soft paraffin, hydrochloric acid (for pH adjustment) and purified water.

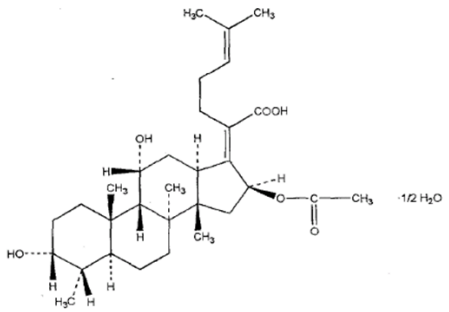
The cream is presented in 15 gram or 30 gram aluminium tubes with a HDPE screw cap.

II.2 Drug Substance

INN: Fusidic acid

Chemical name: *ent*-(17Z)-16α-(Acetyloxy)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid

Structure:



Molecular formula: $C_{31}H_{48}O_6$ 1/2H_2O

Molecular mass: 516.709

All aspects of the manufacture and control of the active substance, fusidic acid, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development of Fusidic Acid 2% Cream was to develop a generic version of the innovator product.

The proposed and the reference products were tested for a number of parameters to support the claim that the products were comparable.

All excipients comply with their European Pharmacopoeia monographs, with the exception of hydrochloric acid, which was controlled by a suitable in-house specification. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

Manufacture of the product
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 and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for product stored in unopened tubes when the storage precaution 'Do not store above 25°C' is applied. Once the tube is first opened the product should be used within 4 weeks.

II.4 Discussion on chemical, pharmaceutical and biological aspects

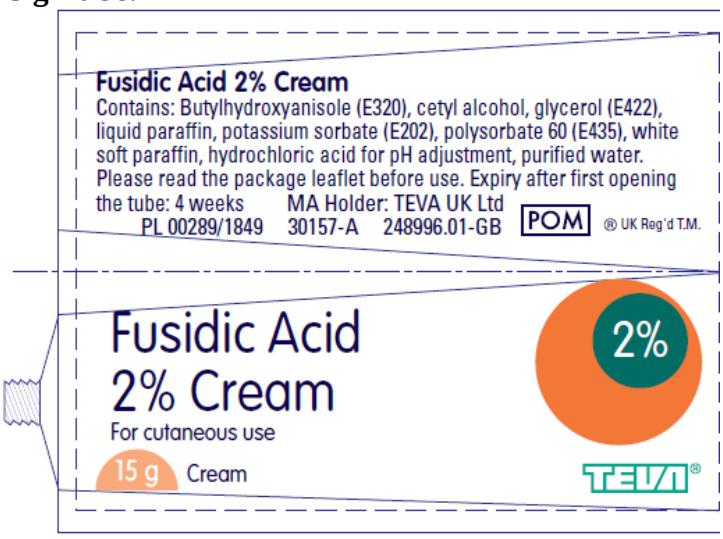
The grant of a marketing authorisation is recommended.

II.5 SmPC, PIL and labelling

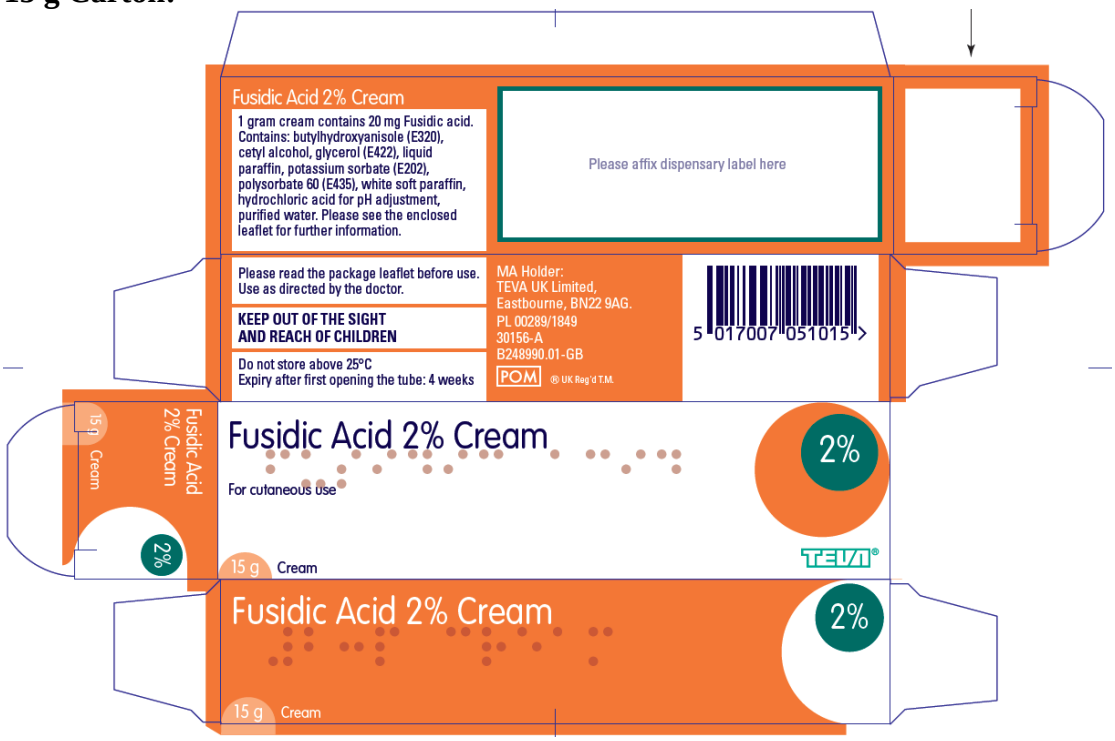
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following product labelling was approved for use in the UK:

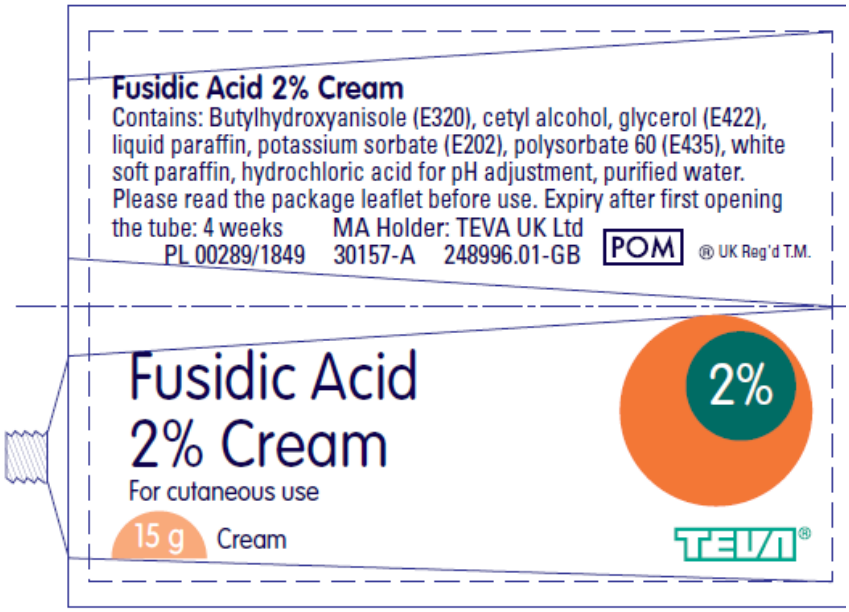
15 g Tube:



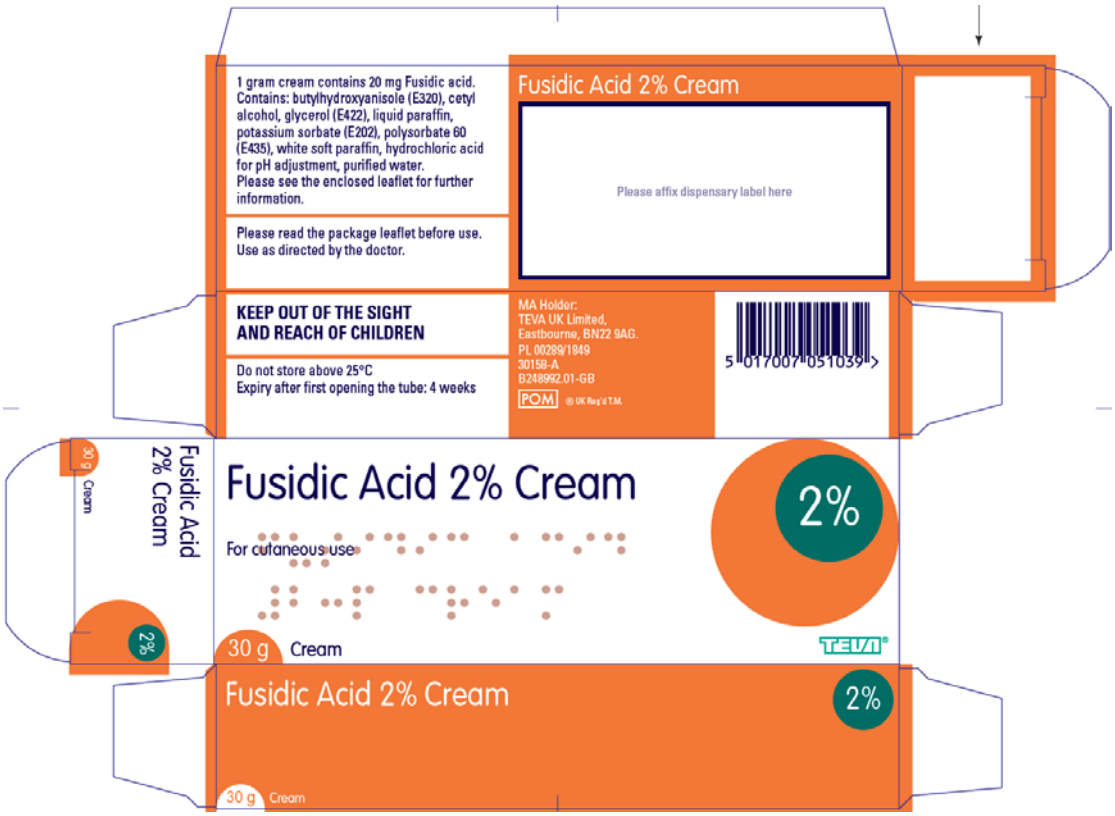
15 g Carton:



30 g Tube:



30 g Carton:



III Non-clinical aspects

No new non-clinical data have been submitted and none are required for an application of this type. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

Since the formulation of Fusidic Acid 2% Cream is intended for generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV Clinical aspects

IV.1 Introduction

The application is supported by a clinical study in patients with impetigo, comparing the proposed product to the reference product.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

IV.3 Pharmacodynamics

No new pharmacodynamic data are required for this application and none have been submitted.

IV.4 Clinical efficacy

The aim of the clinical study was to assess whether the clinical efficacy and safety of the proposed product, Fusidic Acid 2% Cream, and the originator, Fucidin 20mg/g cream, are equivalent in a 7-day treatment of impetigo in adult and paediatric patients.

The clinical study was conducted in the Netherlands, Belgium and Serbia in male and female adults and children aged over18 months with localised *Impetigo contagiosa*, with a skin infection score of >7 points.

Method

At the baseline visit, instructions were given on how to apply the cream, the dose, and frequency of application. The patient was also instructed to record applications, and any influence of impetigo on daily life, in a diary.

Following disinfection of the skin lesions, the test or reference preparation was applied to the affected area of the skin three times daily for two weeks, or until the lesions had disappeared (which ever was sooner). The treated lesions were covered with a gauze dressing and bandage. The amount of cream applied on each occasion was dependent on the size and location of the skin lesion(s) and on the age of the subject.

At the follow up visits after 7 and 14 days the effect of treatment was assessed, the diary was evaluated, and cream usage verified.

Evaluations were conducted at Visit 1 (Day 0: Baseline), Visit 2 (Day 7: Follow-up) and Visit 3 (Day 14: Follow-up). At the baseline visit, in addition to demographic data and medical history, skin lesion characteristics, physical examination, skin infection score and microbiology of the lesions (swabbing with sterile cotton wool swabs followed by microbiological analysis) were recorded.

Nose swabs were taken to check whether the patient was a carrier of *Staph. aureus*. In addition, at the two follow-up visits at weeks 1 and 2, clinical outcome and any adverse events were recorded.

Repeat swabs for microbiological analysis were only taken on these occasions if skin lesions were still present.

For the determination of clinical efficacy after 7 and 14 days, the overall impetigo condition was assessed *i.e.* size and number of all lesions. Cure after one week (defined as the complete absence of lesions or the lesions having become dry and without crusts; residual local erythema of intact skin was acceptable

Four possible endpoints were defined:

1. Cure: defined as the complete absence of lesions or the lesions having become dry and without crusts; remaining local erythema of the intact skin was acceptable, or such progress that no further antibiotic therapy is necessary.

2. Improvement: defined as decline in the affected area, number of lesions or both, as compared to previous visit, such that additional antibiotic therapy is required

3. Failure: insufficient improvement or deterioration (*e.g.* lesions remain crusted and/or have exudate, leaving a yellow or honey coloured crusted lesion, area increases with or without an increase in the number of lesions), as compared to previous visit, such that additional antibiotic therapy is required.

4. Unable to determine: the effect of the treatment is not assessable (*e.g.* subjects who refused informed consent, or who were lost to follow up).

Primary outcome:
Rate of "cure" at one week. At the follow-up visits, the effect of the treatment (*i.e.* clinical efficacy) was assessed:

Secondary outcomes:
Efficacy

- Improvement – reduction in the area affected or number of lesions or both
- Bacterial cure – defined as elimination of causative pathogens in persisting lesions or the unavailability of a swab if the lesion was "cured". Failure: insufficient improvement or deterioration (*e.g.* lesions remain crusted and/or have exudate, leaving a yellow or honey coloured crusted lesion, area increases with or without an increase in the number of lesions), as compared to previous visit, such that additional antibiotic therapy is required.
- Unable to determine: the effect of the treatment is not assessable (*e.g.* subjects who refused informed consent, or who were lost to follow up).

Safety

- Safety evaluation - tolerability and adverse event profiles

Results
177 patients were enrolled but one subject only attended the baseline visit and was then lost to follow-up. Of the remaining 176 subjects 85 were randomised to the proposed product and 91 to the reference product. The safety population comprised 175 patients and the intention to treat (ITT) population at week 1 was 172 and at week 2 was 173 patients. The week one and two per protocol (PP) populations comprised 169 subjects. Reasons for inclusion/exclusion in the ITT and PP analyses are given in the clinical study report and are satisfactory.

The majority of patients completed the full study; 19 were discontinued (9 from the test group and 10 from the reference group). The most common reason for discontinuation was failure to return for one or more follow-up visits. Two subjects in the test group discontinued due to treatment failure and another two in the reference group discontinued due to an adverse event.

Conduct of the study
Patient compliance with the use of study drug was estimated by means of the patient completed diaries. The majority of the patients completed the diaries according to the protocol. The overall mean number ± SD of applications of the study cream was 25.1 ± 11.0. The mean number of applications in the two treatment groups was similar: 25.7 ± 12.1 in the groups treated with the test and reference products. These results are indicative of good overall treatment compliance, and also reflect a comparable compliance in both treatment groups.

Baseline data
The subject demographic characteristics (age, height, body weight) and the distributions of the clinical characteristics of the impetiginous lesions were well-matched between the two groups, with the exception of there being more males in the reference group; male: female 35: 50 on test, 49: 42 on reference treatment. This was not considered to have a bearing on the study results. The mean age (SD) of the subjects was 22.1 (19.8) yr for the test group and 23.2 (20.2) yr for the reference group; other demographic characteristics at baseline (height, body weight) were well-matched between the groups also. The other characteristics of the skin lesions (number of lesions, estimated total lesion area, presence of exudate, crusting, erythema, skin warmth, oedema, itching and pain) were also comparable at baseline and the total skin score was 15.44 (6.57) for the test group and 15.67 (7.35) for the reference group.

Microbiological analysis of the swabs taken from the target skin lesions at baseline showed that a total of 107/169 (63.3%) were positive for *Staph. aureus* when cultured and 13/169 (7.7%) were positive for *Strep. pyogenes*. Other bacteria (not cultured) made up the majority of the remainder of the swab samples and were also present in some mixed cultures with *Staph. aureus* and *Strep. pyogenes*. In the case of seven patients (4.0%) no baseline microbiology result could be obtained. About one-third (26.2%) of *Staph. aureus* cultures were resistant to fusidic acid. The incidence of resistance differed between the Netherlands (40.3%) and Belgium (8.6%). None of the skin samples from the Serbian patients – which were positive for *Staph. aureus* – showed resistance to fusidic acid.

Numbers analysed
A total of 176 subjects were enrolled (85 on the test preparation and 91 on the reference preparation).

The ITT population at week 1 was 172 and at week 2 was173 subjects. The week one and two PP populations were 169 subjects, in both cases. The safety population included 175 patients.

Outcomes and estimation
- **Summary of main efficacy results**

The primary efficacy parameter was the rate of “cure” at one week. The findings are summarised in the table below.

Primary Efficacy Analysis at Week 1 of Treatment (ITT)

	Test	Reference	Totals
No. of subjects	85	87	172
Cured	55 (64.7%)	54 (62.1%)	109 (63.4%)
Improved	26 (30.6%)	29 (33.3%)	55 (32.0%)
Failed	4 (4.7%)	4 (4.6%)	8 (4.7%)

The difference in cure rates at week 1 between test and reference was found to be in favour of the proposed generic product *i.e.* 2.6% (95% CI -11.6 to 16.7%). This was well within the prespecified 20% clinically significant difference between the two products. This indicates that the two products are therapeutically comparable in terms of efficacy.

The week 2 efficacy analysis for the ITT population is shown in the following table.

Efficacy Analysis at Week 2 of Treatment (ITT)

	Test	Reference	Totals
No. of subjects	85	88	173
Cured	74 (87.1%)	77 (87.5%)	151 (87.3%)
Improved	5 (5.9%)	7 (8%)	12 (6.9%)
Failed	6 (7.1%)	4 (4.5%)	10 (5.8%)

The difference in cure rates at week 2 of treatment shows that the proportions for test and reference are 87.1% and 87.5%, respectively. The inter-treatment difference (test-reference) is -0.4% (95% CI -9.8 to 8.9%), again supporting the primary efficacy analysis of equivalence between the two products.

For the PP population, the inter-treatment difference in cure rates at week 1 was 3.8% (95% CI-10.6 to 17.9%). This again supports the ITT results, demonstrating equivalence between test and reference products since the upper bound of the 95% CI is within the 20% pre-specified difference.

Efficacy Analysis at Week 1 of Treatment (PP)

	Test	Reference	Totals
No. of subjects	82	87	169
Cured	54 (65.9%)	54 (62.1%)	108 (63.9%)
Improved	24 (29.3%)	29 (33.3%)	53 (31.4%)
Failed	4 (4.9%)	4 (4.6%)	8 (4.7%)

The week 2 results for the PP populations are shown below.

Efficacy analysis at week 2 of treatment (PP population)

	Test	Reference	Totals
No. of subjects	82	87	169
Cured	72 (87.8%)	77(88.5%)	149 (88.2%)
Improved	4 (4.9%)	6 (6.9%)	10 (5.9%)
Failed	6 (7.3%)	4 (4.6%)	10 (5.9%)

The proportions of patients cured at week 2 in the PP population were 87.8% for the test group and 88.5% for the reference group. This gives an inter-treatment difference of -0.7% (95% CI -9.8 – 8.4%), again confirming equivalence.

The PP findings are therefore consistent with those for the ITT population.

For the number of impetiginous lesions, the scores in the test group changed from a mean (SD) of 3.81 (5.61) at baseline to 1.90 (5.84) at week 1 and to 0.18 (0.63) at week 2. The corresponding scores in the reference group changed from a mean (SD) of 4.21 (3.64) at baseline to 1.67 (3.94) at week 1 and to 0.35 (1.94) at week 2.

In terms of the estimated total lesional area affected by the impetigo in the test group, this was 5.96 (7.29) (mean (SD)) cm^2 at baseline, 2.10 (7.28) cm^2 by week 1 and 0.47 (2.41) cm^2 at week 2. For the reference group, the total lesional area went from a mean (SD) of 7.47 (9.55) at baseline to 2.86 (8.65) at week 1 and 0.25 (1.12) cm^2 at week 2.

The mean (SD) total skin infection scores were 15.44 (6.6) in the test group and 15.67 (7.4) in the reference group at baseline. These decreased to 3.13 (5.3) for test and 2.84 (4.7) for reference by week 1, and to 0.71 (2.5) and 0.47 (1.4), respectively, by week 2.

Bacterial cure

Bacterial cure was assessed as follows: if lesions were cured it was not possible to obtain a skin sample, thus it was assumed that in case of clinical cure there was also bacterial cure. In addition, in case a sample was taken at one of the follow up visits and the microbiology categories “SA”, “SP”, and “other” scored negative, it was regarded as “bacterial cure”.

The tables below summarise the findings per treatment group and country (since resistance to fusidic acid is known to show regional variations)

Bacterial cure after one week per treatment group

Parameter	*Fusidic acid hydrophilic cream 20 mg/g* N=75	Fucidin® cream N=79	Total N=154
Bacterial cure after 1 week	60 (80.0%)	62 (78.5%)	122 (79.2%)
No bacterial cure after 1 week	15 (20.0%)	17 (21.5%)	32 (20.8%)

Bacterial cure after one week per treatment group

Parameter	NL N=78	BE N=63	SE N=13	Total N=154
Bacterial cure after 1 week	53 (67.9%	59 (93.7%)	10 (76.9%)	122 (79.2%)
No bacterial cure after 1 week	25 (32.1%)	4 (6.3%)	3 (23.1%)	32 (20.8%)

Assessor's overall conclusions on clinical efficacy

In conclusion, this study has demonstrated that the test product and the reference product are sufficiently therapeutically comparable for approval of the test product as a hybrid generic medicinal product, in terms of efficacy in the treatment of adults and children with localised impetigo over a two week treatment period.

IV.5 Clinical safety

Introduction

No specific safety studies were conducted by the applicant.

Patient exposure

The duration of exposure to study drug, specified in the protocol, was 14 days or until cure. The table below shows that the number of cream applications, and thus treatment exposure, was comparable in the two treatment groups.

Patient exposure to study treatments

Medication	Test	Reference
Total no. of patients exposed (safety population)	85	90
Nos. patients exposed with adequate diary data	79	89
Mean no. cream applications (SD)	25.7 (12.1)	24.6 (9.9)
Median no. cream applications (IQR)	21.0 (20.0)	21.0 (16.0)

Adverse events

Fourteen subjects (four in the test group and 10 in the reference group) experienced 16 mild or moderate adverse events (total 4 and 12 adverse events, respectively). There were no serious adverse events occurring in the study. The type of recorded adverse event by body system is summarised in the following table.

Type of Adverse Event by Body System

System organ class	Test (n=4)	Reference (n=12)
Infections and infestations	0	6
Skin / subcutaneous tissue disorders	3	2
General disorders and administration site conditions	0	2
Surgical and medical procedures	0	1
Metabolism and nutrition disorders	0	1
Respiratory, thoracic and mediastinal disorders	1	0

The specific adverse events reported in the test group were diaper rash, eczema, epistaxis and plaster allergy. Those reported in the reference group comprised lung infection, cold, influenza, viral throat infection, progression of lesions, tiredness, loss of appetite, tooth extraction, cystitis, rhinitis, and facial eczema. Fourteen of the 16 adverse events were considered to be unrelated or unlikely to be related to the study treatments by the investigator.

One adverse event (progression of lesions) was possibly related and one adverse event (facial eczema) was probably related to the study medication.

Serious adverse events and deaths
In the clinical study no deaths or serious adverse events occurred.

Laboratory findings
In the clinical study no clinically relevant changes were noted. With respect to the vital signs that were investigated, *i.e.* supine pulse, blood pressure, and temperature, there were no relevant differences between treatment groups and there were no clinically relevant changes in the follow up visits.

Vital signs, physical findings and other observations related to safety
In the clinical study there were no clinically significant changes in supine pulse, systolic /diastolic blood pressure and body temperature from baseline to the end of day 7 and day 14 of treatment in either group. There were also no significant differences between the treatment groups in vital signs.

Discontinuation due to adverse events
In the clinical study two subjects in the reference group experienced post-randomisation withdrawals due to adverse events (facial eczema and lung infection).

Post marketing experience
No post-marketing data are available. The medicinal product has not yet been marketed in any country.

Assessor's overall conclusions on clinical safety
The results from the clinical study indicate that the safety and tolerability profile of the proposed test product is comparable to that for the reference product. There was no indication that the adverse event frequency or nature were in any way different to what would be expected from a topical fusidic acid product and, overall, the test product was very well tolerated in adults and children.

IV.6 Risk Management Plan

The applicant has submitted an RMP, 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 2% Cream. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	**Hypersensitivity reactions**
Objective(s) of the risk minimisation measures	To notify treating physician and patients on risk of hypersensitivity reactions and to minimise the risk.
Routine risk minimisation measures	(Proposed) text in SmPC: 4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. 4.4 Special warnings and precautions for use Extended or recurrent use may increase the risk of developing contact sensitisation. 4.8 Undesirable effects The most frequently reported adverse reactions during treatment are various skin reactions such as pruritis and rash, followed by application site conditions such as pain and irritation reactions, which all occurred in less than 1% of patients. Hypersensitivity and angioedema have been reported. • Rare: Hypersensitivity, Angioedema, Urticaria, Blister • Uncommon: Pruritus; Rash (various types of rash reactions such as erythematous, pustular, vesicular, maculo-papular and popular have been reported. Rash generalised has also occurred)
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures None proposed
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The success of the proposed routine risk minimisation activities will be indirectly measured by monitoring spontaneous reports relating to the events captured via post-marketing safety surveillance.
Criteria for judging the success of the proposed risk minimisation measures	As part of the routine pharmacovigilance, the applicant will investigate any potential safety signal identified both quantitatively (e.g., PRR (proportional reporting ratio) and qualitatively (e.g., literature).

Safety concern	**Hypersensitivity reactions**
Planned dates for assessment	Periodic review.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Safety concern	**Exposure of breast-fed infants**
Objective(s) of the risk minimisation measures	To minimise the risk.
Routine risk minimisation measures	(Proposed) text in SmPC: 4.6 Fertility, pregnancy and lactation Topical fusidic acid can be used during breast-feeding but it is recommended to avoid applying topical fusidic acid on the breast.
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures None proposed
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The success of the proposed routine risk minimisation activities will be indirectly measured by monitoring spontaneous reports relating to the events captured via post-marketing safety surveillance.
Criteria for judging the success of the proposed risk minimisation measures	As part of the routine pharmacovigilance, the applicant will investigate any potential safety signal identified both quantitatively (e.g., PRR (proportional reporting ratio) and qualitatively (e.g., literature).
Planned dates for assessment	Periodic review.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Safety concern	**Resistant bacterial infection**
Objective(s) of the risk minimisation measures	To notify treating physician and patients and to minimise the potential risk.
Routine risk minimisation measures	(Proposed) text in SmPC: 4.4 Special warnings and precautions for use Bacterial resistance among staphylococcus aureus has been reported to occur with the use of topical fusidic acid. As with all antibiotics, extended or recurrent use may increase the risk of developing antibiotic resistance. 5.1 Pharmacodynamic properties Information on resistance mechanism is provided in this section.
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures None proposed
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The success of the proposed routine risk minimisation activities will be indirectly measured by monitoring spontaneous reports relating to the events captured via post-marketing safety surveillance.
Criteria for judging the success of the proposed risk minimisation measures	As part of the routine pharmacovigilance, the applicant will investigate any potential safety signal identified both quantitatively (e.g., PRR (proportional reporting ratio) and qualitatively (e.g., literature).
Planned dates for assessment	Periodic review.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Safety concern	**Contact sensitisation with extended use times**
Objective(s) of the risk minimisation measures	To notify treating physician and patients on risk and to minimise the potential risk.
Routine risk minimisation measures	(Proposed) text in SmPC: 4.4 Special warnings and precautions for use Extended or recurrent use may increase the risk of developing contact sensitisation.
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures

Safety concern	**Contact sensitisation with extended use times**
	None proposed
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The success of the proposed routine risk minimisation activities will be indirectly measured by monitoring spontaneous reports relating to the events captured via post-marketing safety surveillance.
Criteria for judging the success of the proposed risk minimisation measures	As part of the routine pharmacovigilance, the applicant will investigate any potential safety signal identified both quantitatively (e.g., PRR (proportional reporting ratio) and qualitatively (e.g., literature).
Planned dates for assessment	Periodic review.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Safety concern	**Irritation through accidental ocular exposure**
Objective(s) of the risk minimisation measures	To notify treating physician and patients on risk of hypersensitivity reactions and to minimise the potential risk.
Routine risk minimisation measures	(Proposed) text in SmPC: 4.4 Special warnings and precautions for use Fusidic acid 20 mg/g cream contains butylhydroxyanisole, cetyl alcohol and potassium sorbate which may cause local skin reactions (e.g. contact dermatitis). Butylhydroxyanisole may also cause irritation to the eyes and mucous membranes. <Invented name> should therefore be used with care when applied to the proximity of the eyes. 4.8 Undesirable effects Rare: Conjunctivitis
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures None proposed
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the	The success of the proposed routine risk minimisation activities will be indirectly measured by monitoring spontaneous reports relating

Safety concern	Irritation through accidental ocular exposure
safety concern will be measured	to the events captured via post-marketing safety surveillance.
Criteria for judging the success of the proposed risk minimisation measures	As part of the routine pharmacovigilance, the applicant will investigate any potential safety signal identified both quantitatively (e.g., PRR (proportional reporting ratio) and qualitatively (e.g., literature).
Planned dates for assessment	Periodic review.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

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 Dutch.

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.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fusidic acid is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)