Public Assessment Report

Decentralised Procedure

Fusidic Acid Cream 20 mg/g Cream

Procedure No: UK/H/3764/001/DC

UK Licence No: PL 34372/0001

Basic Pharma Manufacturing BV
LAY SUMMARY

On 20 January 2012 the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Basic Pharma Manufacturing BV for the medicinal product Fusidic acid 20 mg/g cream (PL 34372/0001; UK/H/3764/001/DC). This is a prescription-only medicine (POM) used for the local 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).

The active ingredient in Fusidic acid 20 mg/g cream is fusidic acid, which is an antibiotic (this means that it kills bacteria that cause infections).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Fusidic acid 20 mg/g cream outweigh the risks; therefore, a Marketing Authorisation has been granted.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Fusidic acid 20 mg/g cream</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid, Article 10.3</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Fusidic acid</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Cream</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>20 mg/g</td>
</tr>
</tbody>
</table>
| **MA Holder**            | Basic Pharma Manufacturing B.V.  
Burg. Lemmensstraat 352  
6163 JT Geleen  
The Netherlands |
| **Reference Member State (RMS)** | UK                      |
| **Concerned Member States (CMS)** | Belgium, Germany, Luxembourg, the Netherlands and Poland |
| **Procedure Number**     | UK/H/3764/001/DC          |
| **Timetable**            | Day 210 – 01 December 2011 |
Module 2
Summary of Product Characteristics

The text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Focus Pharmaceuticals Limited at the earliest opportunity. Hence, there is no UK Specific Product Licence number on the SmPC or the labelling at this time. The Marketing Authorisation Holder has provided an assurance that the product will not be marketed until the Change of Ownership has been completed.

1 NAME OF THE MEDICINAL PRODUCT

{Fusidic acid [Company Name] 20 mg/g cream}  {To be completed nationally}

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 20 mg fusidic acid.

Excipient(s): Contains Butylhydroxyanisole 0.04 mg/gram, Cetyl alcohol 111.00 mg/gram, and Potassium sorbate 2.70 mg/gram

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.
White, homogenous cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of non-severe, superficial, non-extensive, primary skin infections caused by microorganisms that are sensitive to fusidic acid, especially of infections caused by *Staphylococcus* (see section 5.1).

Primary skin infections that may be expected to respond to treatment with fusidic acid applied topically include: impetigo contagiosa, superficial folliculitis, sycosis barbae, paronychia and erythrasma.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

**Posology**

**Adults and children:**
Uncovered lesions: apply gently three or four times daily.

Covered lesions: less frequent applications may be adequate.

**Method of administration:**
Cutaneous use

4.3 Contraindications

Fusidic acid 20 mg/g cream is contraindicated in patients with known hypersensitivity to fusidic acid or to any of the excipients used in the product.

4.4 Special warnings and precautions for use

Bacterial resistance has been reported to occur with the use of fusidic acid. As with all antibiotics, extended or recurrent use may increase the risk of developing antibiotic resistance.

Fusidic acid should not be used in infections caused by non-susceptible organisms, in particular, *Pseudomonas aeruginosa*, see section 5.1.

Extended or recurrent use may increase the risk of developing contact sensitisation.

When Fusidic acid 20 mg/g cream is used on the face, care should be taken to avoid the eyes, because fusidic acid can cause irritation of the conjunctiva.
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.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is inadequate evidence of safety in human pregnancy. Animal studies and many years of clinical experience have suggested that fusidic acid is devoid of teratogenic effect. There is evidence to suggest that when given systemically, fusidic acid can penetrate the placental barrier. The use of topical Fusidic acid 20 mg/g cream in pregnancy requires that the potential benefits be weighed against the possible hazards to the foetus.

Breastfeeding
Safety in nursing mothers has not been established. When fusidic acid (as the sodium salt) has been given systemically, levels have been detected in breast milk, but with topical use the possible amount of drug present is unlikely to affect the infant.

4.7 Effects on ability to drive and use machines
Fusidic acid cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
The most frequently reported adverse drug reactions are various skin reactions and in particular application site reactions.

Undesirable effects are listed by MeDRA SOC and the individual undesirable effects are listed starting with the most frequently reported.

- Very common \( \geq 1/10 \)
- Common \( \geq 1/100 \) and <1/10
- Uncommon \( \geq 1/1,000 \) and <1/100
- Rare \( \geq 1/10,000 \) and <1/1,000
- Very rare <1/10,000

Not known (cannot be estimated from the available data).

Side effects are classified according to organ system, and within each organ, grouped by frequency.

**Immune system disorders**
- Rare
  - Hypersensitivity

**Eye disorders**
- Rare
  - Conjunctivitis

**Skin and subcutaneous tissue disorders**
- Uncommon:
  - Pruritus
  - Rash including erythematous, maculo-papular and pustular reactions
  - Contact Dermatitis
  - Irritation at site of application (including pain, stinging, burning and erythema)

- Not known:
  - Urticaria
  - Angiodema
  - Eczema
  - Periorbital oedema

4.9 Overdose
Overdose is unlikely.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antibiotics for topical use, ATC code: D06AX01

Active mechanism:
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.

As it is the only type of drug available in this family of drugs, there have been no reports of cross resistance to fusidic acid.

Resistance mechanism(s):
Resistance for fusidic acid can vary geographically and information about local resistance patterns should be obtained through a local microbiology laboratory. In general, resistance occurs in 1-10 % of Staphylococcus aureus and 10-20 % of coagulase negative staphylococcus. Cross-resistance between Fusidic acid hydrophilic cream 20 mg/g and other antibiotics has not been reported.

Breakpoints:
The following MIC values are recommended to distinguish sensitive and non-sensitive germs: S \leq 1 \mu g/ml and R > 1 \mu g/ml. This breakpoint should be used for the systemic use of fusidic acid. In general, no breakpoints are established for the topical use of antibiotics.

Sensitivity:
The sensitivity of organisms to fusidic acid is based on the in vitro sensitivity and plasma concentrations that are achieved after systemic therapy. Local treatment causes higher peak concentrations as compared to plasma. However, it is not known how the kinetics of the cream after local application may change the effectiveness of the cream.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
<th>Staphylococcus aureus and Staphylococcus epidermis (including methicillin resistant and beta lactamase producing strains); Corynebacterium minutissimum; Clostridium spp.; Peptococcus spp.; Peptostreptococcus spp.; Neisseria spp.; Bacteroides fragilis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherently resistant organisms</td>
<td>Streptococcus pyogenes; Streptococcus pneumoniae; Streptococci viridans; most gram negative bacilli including Haemophilus influenza; Enterobactereaceae; Pseudomonas spp.; Escherichia coli and Klebsiella pneumoniae.</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties
In Vitro studies show that fusidic acid can penetrate intact human skin. The degree of penetration depends on factors such as the duration of exposure to fusidic acid and the condition of the skin. Fusidic acid is excreted mainly in the bile with little excreted in the urine.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Butylhydroxyanisole (E 320)
Cetyl alcohol
Glycerol (85%)
Liquid paraffin
Potassium sorbate (E 202)
Polysorbate 60
White soft paraffin
Hydrochloric acid for pH adjustment
Purified water

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
Unopened tube: 3 years.
After opening of the tube: 4 weeks.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Aluminium tube with HDPE screw cap.
Pack sizes: 15 gram and 30 gram.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Basic Pharma Manufacturing B.V.
Burg. Lemmensstraat 352
6163 JT Geleen
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT
Module 3

The leaflet text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Focus Pharmaceuticals Limited at the earliest opportunity. The Marketing Authorisation Holder has provided an assurance that the product will not be marketed until the Change of Ownership has been completed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

{Fusidic acid [Company Name] 20 mg/g cream}  {To be completed nationally}

Fusidic Acid

Read all of this leaflet carefully before you start using this medicine

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What {Fusidic acid cream} is and what it is used for
2. Before you use {Fusidic acid cream}
3. How to use {Fusidic acid cream}
4. Possible side effects
5. How to store {Fusidic acid cream}
6. Further information

1. WHAT {FUSIDIC ACID CREAM} IS AND WHAT IT IS USED FOR

The active ingredient of {Fusidic acid cream} is fusidic acid. This is an antibiotic (this means that it kills bacteria that cause infections).

{Fusidic acid cream} should be used on the skin. The cream is used for the local 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, erythrasma (infection with brown, scaly skin patches, especially in the folds of the body).

2. BEFORE YOU USE {FUSIDIC ACID CREAM}

Do not use {Fusidic acid cream} if you are allergic (hypersensitive) to fusidic acid or any of the other ingredients of {Fusidic acid cream}. Therefore, always tell your doctor which medicines or other substances you are allergic to.

Take special care with {Fusidic acid cream}
• if you use {Fusidic acid cream} on the face. The cream should not be applied in or near the eye because it can lead to a prickling feeling in the eye.
• if you use the cream for a long time or in large amounts as it may make the chance of getting any side effects higher. Also your skin may get more sensitive to the cream.

Please tell your doctor if one of the above warnings applies to you or has applied to you in the past.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There is no known effect of (Fusidic acid cream} with other medicines.

Pregnancy and breast-feeding

Pregnancy:
There is not enough evidence to say that it is safe to use {Fusidic acid cream} during pregnancy.
You need to discuss your specific circumstances with your doctor to weigh up the overall risks and benefits of using this medicine. You and your doctor can make a decision about whether you are going to use this medicine during pregnancy.
You should only use this medicine during pregnancy if your doctor thinks that you need it.

Breast-feeding:
There is not enough evidence to say that it is safe to use {Fusidic acid cream} while breast-feeding. However, using {Fusidic acid cream} topically and breast-feeding is unlikely to harm your baby.
You should only breast-feed your baby while using this medicine on the advice of your doctor.

Ask your doctor or pharmacist for advice before taking any medicine!

Driving and using machines
This cream does not affect your ability to drive or operate machinery.

Important information about some of the ingredients of {Fusidic acid cream}
{Fusidic acid 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.

3. HOW TO USE {FUSIDIC ACID CREAM}

Always use {Fusidic acid cream} exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage
Your doctor will tell you how much {Fusidic acid cream} you should use.

Adults and children
Usually a small amount of cream is applied to the infected skin three or four times each day. If your doctor advises you to use a sterile bandage or dressing, you usually can reduce the number of applications.
A nappy on a baby may act as a dressing. Follow the advice of your doctor.

If you think that the effect of {Fusidic acid cream} is too strong or too weak, ask your doctor or pharmacist for advice.

**How to apply {Fusidic acid cream}**

{Fusidic acid cream} should be applied to the skin. Do not swallow it.

1. Always wash your hands before you use the cream.
2. Remove the cap.
3. Check that the seal is not broken before you use the cream for the first time.
4. Push the spike in the cap through the seal of the tube.
5. Rub the cream gently on the skin.
6. If you use the cream on your face be careful to avoid your eyes.
7. Always wash your hands after using the cream, unless you are using the cream to treat your hands.

If you accidentally get any cream in your eye, wash it out with cold water straight away. Then rinse your eye with eye wash if possible. Your eye may sting. If you start to have any problems with your sight or your eye is sore, contact your doctor immediately.

**Duration of treatment**

The duration of the treatment will be decided by your doctor. Treatment is usually 1 to 2 weeks, although it may be longer. This depends on the type of infection and the result of the treatment. Take special care if you use the cream for a long time or in large amounts, because then there is a higher chance of getting side effects. Therefore, always follow the advice of your doctor.

**If you use more {Fusidic acid cream} than you should**

If you apply too much or accidentally swallow {Fusidic acid cream}, it is unlikely to cause any harm. However, if you notice any effect or are worried, contact your doctor or pharmacist. You should contact the doctor if {Fusidic acid cream} is accidentally swallowed by an infant.

**If you forget to use {Fusidic acid cream}**

If you forget to use the cream, apply the usual amount of {Fusidic acid cream} as soon as you remember. Do not apply a double dose to make up for a forgotten dose.

**If you stop using {Fusidic acid cream}**

Always use {Fusidic acid cream} for duration directed by your doctor. Speak to your doctor if unsure. If you stop using {Fusidic acid cream} prematurely, it is possible that the skin infection returns or does not cure.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, {Fusidic acid cream} can cause side effects, although not everybody gets them.

The most frequently reported side effects are various skin reactions and in particular application site reactions.
The frequency of occurrence of side effects is as follows:

**Very common:** Affects more than 1 in 10 users
**Common:** Affects up to 1 in 10 users
**Uncommon:** Affects up to 1 in 100 users
**Rare:** Affects up to 1 in 1,000 users
**Very rare:** Affects up to 1 in 10,000 users
**Not known:** Frequency cannot be estimated from the available data

### Uncommon

**Skin and subcutaneous tissue disorders**
- Itching
- Rash
- Skin sensitivity reactions (contact dermatitis)
- Irritation at site of application (including pain, stinging, burning and redness of the skin)

### Rare

**Immune system disorders**
- You must get urgent medical help if you have any of the following symptoms.
  - You have difficulty breathing
  - Your face or throat swell
  - Your skin develops a severe rash.

**Eye disorders**
- Inflammation of the eye (conjunctivitis)

### Not known

- Hives
- Angioedema (sudden swelling in the skin and mucous membranes (for example throat and tongue), breathing problems and/or itching and skin rash, often the symptoms of an allergic reaction)
  - Immediately contact your doctor or pharmacist if this occurs.
- Eczema
- Sudden swelling around the eyes (periorbital oedema)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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5. **HOW TO STORE {FUSIDIC ACID CREAM} 20 MG/G**

Keep out of the reach and sight of children.

Do not use {Fusidic acid cream} after the expiry date which is stated on the carton or the tube after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25°C.
Discard the tube after 4 weeks of first opening the tube even if there is still some cream left in it.
6. FURTHER INFORMATION

What {Fusidic acid cream} contains

- The active substance is fusidic acid. Each gram of cream contains 20 mg fusidic acid.
- The other ingredients are butylhydroxyanisole (E320), cetyl alcohol, glycerol (E422), liquid paraffin, potassium sorbate (E202), polysorbate 60 (E435), white soft paraffin, hydrochloric acid for pH adjustment, purified water. Some of these ingredients can cause a skin reaction, see section 2 of this leaflet.

What {Fusidic acid cream} looks like and contents of the pack
{Fusidic acid cream} is a white to off-white cream, and is available in an aluminium tube with HDPE screw cap.

Pack sizes: 15 gram and 30 gram.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Basic Pharma Manufacturing bv
Burgemeester Lemmensstraat 352
6163 JT Geleen
The Netherlands
Tel: +31 (0)88-2554010
Fax: +31 (0)88-2554098
E-mail: info@basicpharma.nl

This medicinal product is authorised in the Member States under the following names:
Belgium: Affusine
Germany: Fusidinsäure Basic Pharma 20 mg/g Creme
Luxembourg: Affusine
The Netherlands: Fusidinezuur Basic Pharma 20 mg/g crème
Poland: Hylosept
United Kingdom: Fusidic acid 20 mg/g cream

This leaflet was last approved in {MM/YYYY}.
Module 4

The labelling text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Focus Pharmaceutical Limited at the earliest opportunity. Hence, there is no UK Specific Product Licence number on the SmPC or the labelling at this time. The Marketing Authorisation Holder has provided an assurance that the product will not be marketed until the Change of Ownership has been completed.

**PARTICULARS TO APPEAR ON <THE OUTER PACKAGING>**

<table>
<thead>
<tr>
<th>Outer carton</th>
</tr>
</thead>
</table>

**1. NAME OF THE MEDICINAL PRODUCT**

{Fusidic acid [Company Name] 20 mg/g cream} {To be completed nationally}

Fusidic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 gram cream contains 20 mg Fusidic acid.

**3. LIST OF EXCIPIENTS**

Contains: Butylhydroxyanisol (E320), Cetyl alcohol, Glycerol 85%, Liquid paraffin, Potassium sorbate (E202), Polysorbate 60, White soft paraffin, Hydrochloric acid for pH adjustment, Purified water.

See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

<table>
<thead>
<tr>
<th>Cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 gram</td>
</tr>
<tr>
<td>30 gram</td>
</tr>
</tbody>
</table>

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For cutaneous use.

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Expiry after first opening the tube: 4 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Basic Pharma Manufacturing
Burg. Lemmensstraat 352
6163 JT Geleen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{Fusidic acid 20 mg/g cream} {To be completed nationally}
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Aluminium tube

---

1. **NAME OF THE MEDICINAL PRODUCT**

{Fusidic acid [Company Name] 20 mg/g cream}  {To be completed nationally}

Fusidic acid

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 gram cream contains 20 mg Fusidic acid.

3. **LIST OF EXCIPIENTS**

Contains: Butylhydroxyanisol (E320), Cetyl alcohol, Glycerol 85%, Liquid paraffin, Potassium sorbate (E202), Polysorbate 60, White soft paraffin, Hydrochloric acid for pH adjustment, Purified water.  
See package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Cream
15 gram
30 gram

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For cutaneous use.  
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

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8. **EXPIRY DATE**

EXP  
Expiry after first opening the tube: 4 weeks.
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25 °C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Basic Pharma Manufacturing  
Burg. Lemmensstraat 352  
6163 JT Geleen  
The Netherlands

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Fusidic acid 20 mg/g cream (PL 34372/0001; UK/H/3764/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the treatment of non-severe, superficial, non-extensive, primary skin infections caused by microorganisms that are sensitive to fusidic acid, especially of infections caused by Staphylococcus. Primary skin infections that may be expected to respond to treatment with fusidic acid applied topically include: impetigo contagiosa, superficial folliculitis, sycoisis barbae, paronychia and erythrasma.

The active ingredient, fusidic acid, is an antibiotic (this means that it kills bacteria that cause infections).

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Germany, Luxembourg, the Netherlands and Poland as Concerned Member States (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Fucidin 20 mg/g Cream (Leo Pharma AS, Denmark) which was authorised in Denmark on 04 May 1962. The corresponding reference product in the UK is Fucidin Cream (Leo Laboratories Limited, UK) first authorised in the UK on 14 August 1979.

No new non-clinical data have been submitted, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years.

The Marketing Authorisation Holder submitted a non-inferiority study comparing the clinical efficacy and safety of the test product Fusidic acid 20 mg/g cream (Basic Pharma Manufacturing BV, The Netherlands) versus the reference product Fucidin 20 mg/g cream (Leo Pharma, The Netherlands). With the exception of this study, no new clinical data were submitted and none were required for this application as fusidic acid is a well-established active ingredient 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 at all sites responsible for the manufacture, assembly and batch release 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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 01 December 2011. After a subsequent national phase, a licence was granted in the UK on 20 January 2012.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Fusidic acid 20 mg/g cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the active substance(s) (INN)</td>
<td>Fusidic acid</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antibiotics for topical use (D06AX01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Cream</td>
</tr>
<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/3764/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Belgium, Germany, Luxembourg, the Netherlands and Poland</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 34372/0001</td>
</tr>
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| Name and address of the authorisation holder      | Basic Pharma Manufacturing B.V.  
Burg. Lemmensstraat 352  
6163 JT Geleen  
The Netherlands |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Fusidic acid
Chemical name: \( \text{ent-(17Z)-16\alpha-(Acetyloxy)-3\beta,11\beta-dihydroxy-4\beta,8,14-\text{trimethyl-18-nor-5\beta,10\alpha-cholesta-17(20),24-dien-21-oic acid}} \)

Structure:

![Structure of Fusidic Acid](image)

Molecular formula: \( \text{C}_{31}\text{H}_{48}\text{O}_{6} \cdot \frac{1}{2}\text{H}_{2}\text{O} \)
Molecular mass 525.7
Appearance: A white or almost white crystalline powder, practically insoluble in water, freely soluble in alcohol.

Fucidic acid is the subject of a European Pharmacopoeia monograph.

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

Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients butyloxyanisole (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. Appropriate justification for the inclusion of each excipient has been provided.
All excipients comply with their respective European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to produce a safe, efficacious, product that was comparable in performance to the originator product, Fucidin 20 mg/g Cream (Leo Pharma)

The physico-chemical properties of the drug product and the reference product Fucidin 20 mg/g Cream (Leo Pharma) have been found to be comparable.

Suitable pharmaceutical development data have been provided for this application.

**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.

**Control of Finished Product**

The finished product specification is satisfactory. Test methods have been described and 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.

**Container-Closure System**

The finished product is supplied in aluminium tubes fitted with high-density polyethylene screw caps. Each tube contains 15 grams or 30 grams of cream and is packaged into a cardboard carton with a Patient Information Leaflet.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

**Stability of the 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 4 weeks for the opened tube, with the storage conditions “Do not store above 25°C.”

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and, Labelling**

The SmPC, PIL and labelling are acceptable from a pharmaceutical perspective. Final text versions of the labelling and PIL have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities, as appropriate. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive
2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

**MAA form**
The MAA form is satisfactory.

**Expert report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of fusidic acid are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS
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.

Efficacy
With the exception of the data provided in the study below, no new efficacy data have been submitted and none are required.

The following therapeutic equivalence (non-inferiority) study was submitted to support this application.

A multicenter, 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) versus the reference product Fucidin 20 mg/g Cream (Leo Pharma 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:

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<th>Clinical Efficacy Parameter</th>
<th>Fusidic acid 20 mg/g (Test) N=85</th>
<th>Fucidin 20 mg/g (Reference) N=87</th>
<th>Total N=172</th>
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<tr>
<td>Cured</td>
<td>55 (64.7%)</td>
<td>54 (62.1%)</td>
<td>109 (63.4%)</td>
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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 applicant has provided suitable justification for the proposed 20% non-inferiority margin. Hence non-inferiority of the proposed product in comparison to Fucidin 20mg/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 UK, therapeutic equivalence has also been shown between the proposed product Fusidic acid 20 mg/g cream (Basic Pharma Manufacturing BV) and the UK reference product Fucidin Cream (Leo Laboratories Limited, UK).
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.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and is in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Fusidic acid 20 mg/g cream are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
Non-inferiority of this product in comparison to Fucidin 20 mg/g Cream (Leo Pharma BV, The Netherlands) has been established, with no statistically/clinically significance differences observed between products. As the reference product used in the therapeutic equivalence study is considered identical to the reference product in the UK, therapeutic equivalence has also been shown between the proposed product Fusidic acid 20 mg/g cream (Basic Pharma Manufacturing BV, The Netherlands) and the UK reference product Fucidin Cream (Leo Laboratories Limited, UK).

SAFETY
No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the originator product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The therapeutic equivalence study support the claim that the applicant’s product is non-inferior to Fucidin 20 mg/g Cream (Leo Pharma BV, The Netherlands). Extensive clinical experience with fusidic acid is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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