Public Assessment Report

Decentralised Procedure

Xemacort 20 mg/g + 1 mg/g cream

(fusidic acid and betamethasone valerate)

Procedure No: UK/H/5387/001/DC

UK Licence No: PL 04569/1625

Generics [UK] Limited t/a Mylan
LAY SUMMARY

Xemacort 20 mg/g + 1 mg/g cream
(fusidic acid and betamethasone valerate)

This is a summary of the public assessment report (PAR) for Xemacort 20 mg/g + 1 mg/g cream (PL 04569/1625; UK/H/5387/001/DC). It explains how Xemacort 20 mg/g + 1 mg/g 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 Xemacort 20 mg/g + 1 mg/g cream.

For practical information about using Xemacort 20 mg/g + 1 mg/g cream, patients should read the package leaflet or contact their doctor or pharmacist.

What is Xemacort 20 mg/g + 1 mg/g cream and what is it used for?
The application for Xemacort 20 mg/g + 1 mg/g cream was submitted as a hybrid medicine. Assessment of the application concluded that the cream is similar to a reference medicine containing same active substances (fusidic acid and betamethasone valerate) in the same dose.

The reference medicine for Xemacort 20 mg/g + 1 mg/g cream is Fucibet 2%/0.1% cream (Leo Laboratories Ltd; PL 00043/0091).

Xemacort cream is used to treat conditions where the skin is inflamed (eczema or dermatitis) and also infected by germs (bacteria).

How is Xemacort 20 mg/g + 1 mg/g cream used?
Usually a small amount of cream is gently applied to the infected skin twice each day (in the morning and evening). 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 up to two weeks and if no improvement is noticed after seven days, patients should stop using the cream.

Xemacort 20 mg/g + 1 mg/g cream can only be obtained on prescription from a doctor.

For further information on how Xemacort 20 mg/g + 1 mg/g cream is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How does Xemacort 20 mg/g + 1 mg/g cream work?
Xemacort 20 mg/g + 1 mg/g cream contains two active ingredients: fusidic acid, which is an antibiotic that kills bacteria that cause infections, and betamethasone valerate, which is a corticosteroid (steroid) that reduces any swelling, redness or itchiness of the skin.
**What benefits of Xemacort 20 mg/g + 1 mg/g cream have been shown in studies?**

Because the application for Xemacort 20 mg/g + 1 mg/g cream was submitted as a hybrid application and is considered to be therapeutically equivalent to the reference product, Fucibet 2%/0.1% cream, its benefits and risks are taken as being the same as those of the reference medicine.

To support the application for Xemacort 20 mg/g + 1 mg/g cream the Marketing Authorisation Holder has provided a fully validated clinical pharmacodynamic (skin blanching, cutaneous vasoconstriction) study for the corticosteroid (betamethasone) component, a series of *in-vitro* assays for the antibiotic (fusidic acid) component of the cream, and extensive evidence of equivalence with respect to drug product quality.

**What are the possible side effects from Xemacort 20 mg/g + 1 mg/g cream?**

Like all medicines, Xemacort cream can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Xemacort 20 mg/g + 1 mg/g cream, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

**Why is Xemacort 20 mg/g + 1 mg/g cream approved?**

The MHRA decided that the benefits of Xemacort 20 mg/g + 1 mg/g cream are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Xemacort 20 mg/g + 1 mg/g cream?**

A Risk Management Plan (RMP) has been developed to ensure Xemacort 20 mg/g + 1 mg/g 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 Xemacort 20 mg/g + 1 mg/g 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 Xemacort 20 mg/g + 1 mg/g cream**

Belgium, Denmark, Germany, Greece, Italy, Portugal, Republic of Ireland, Spain and the UK agreed to grant a Marketing Authorisation for Xemacort 20 mg/g + 1 mg/g cream on 24 February 2015. A Marketing Authorisation was granted in the UK on 23 March 2015.

For more information about treatment with Xemacort 20 mg/g + 1 mg/g cream, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Xemacort 20 mg/g + 1 mg/g cream follows this summary.

This summary was last updated in January 2016.
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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 Xemacort 20 mg/g + 1 mg/g cream (UK/H/5387/001/DC; PL 04569/1625) was approvable.

The product is a prescription-only medicine (POM) indicated for the treatment of eczematous dermatoses, including atopic eczema, infantile eczema (children of 1 year and over), discoid eczema, stasis eczema, contact eczema, and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Denmark, Germany, Greece, Italy, Portugal, Republic of Ireland, Spain as Concerned Member States (CMSs). The application was made under Article 10.3 of Directive 2001/83/EC, as amended; a hybrid application. The Marketing Authorisation was originally granted to Goapharma SAS (PL 41693/0001) on 23 March 2015. The licence underwent a change of ownership procedure to the current Marketing Authorisation Holder, Generics [UK] Limited t/a Mylan (PL 04569/1625), on 7 May 2015. The reference medicinal product for this application is Fucibet 2%/0.1% cream, which was first authorised to Leo Laboratories Limited (PL 00043/0091) on 27 October 1983. The reference product has been authorised in the European Union for at least 10 years, therefore, the legal basis of this application is acceptable.

Xemacort 20 mg/g + 1 mg/g cream combines the well-known anti-inflammatory and antipruritic effects of betamethasone with the potent topical antibacterial action of fusidic acid. Betamethasone valerate is a topical steroid rapidly effective in those inflammatory dermatoses which normally respond to this form of therapy. More refractory conditions can often be treated successfully. When applied topically, fusidic acid is effective against Staphylococcus aureus, Streptococci, Corynebacteria, Neisseria and certain Clostridia and Bacteroides.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type 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.

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.

No new non-clinical data were submitted, which is acceptable given that the application was based on being a hybrid medicinal product of an originator product that has been in clinical use for over 10 years.
For this type of application, the Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing known constituents (CPMP/EWP/239/95 final) states that data requirements may consist of pharmacodynamic studies, or local availability studies, or possibly *in vitro* studies.

At pre-submission scientific advice meetings, between the Marketing Authorisation Holder and the MHRA, it was agreed that the demonstration of pharmaceutical equivalence (with respect to qualitative, quantitative and physicochemical properties), together with a series of *in vivo* and *in vitro* studies, including pharmacodynamic studies, might be sufficient to predict therapeutic equivalence between Xemacort 20 mg/g + 1 mg/g cream and the reference medicinal product Fucibet 2%/0.1% cream.

The Marketing Authorisation Holder submitted a dossier in accordance with scientific advice.

Robust evidence of a high degree of pharmaceutical equivalence was demonstrated, between test and innovator products, including similarity in quantitative and qualitative composition of the product ingredients and microstructural similarity, despite the complexity of these semi-solid formulations.

A fully validated clinical pharmacodynamic (skin blanching) study for the corticosteroid component has been supplied and was considered sufficient for demonstration of cutaneous bioequivalence of the corticosteroid component.

A portfolio of surrogate *in vitro* studies has also been supplied that aim to inform cutaneous bioequivalence for the antibiotic (fusidic acid) component. These include an *in vitro* release study across a synthetic membrane; an *in vitro* skin permeation study and an *in vitro* skin infection study.

The waiver from a requirement for clinical studies for the fusidic acid (antibiotic) component of the cream was referred to the Chemistry, Pharmacy and Standards Expert Advisory Group (CPS-EAG) on 17th June 2014 and to the Commission on Human Medicines (CHM) on 19th June 2014.

The Commission and the CPS-EAG concluded, for this specific application due to the extensive evidence of a high degree of pharmaceutical equivalence and the *in vitro* studies having been adequately well-conducted, that these data were sufficient to complete the package of critical performance attributes from which, collectively, therapeutic equivalence could be inferred.

The RMS considers that the pharmacovigilance system, as described by the Marketing Authorisation 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 Marketing Authorisation Holder has provided a Risk Management Plan (RMP).

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 209 – 24 February 2015). After a subsequent
national phase, the UK granted a Marketing Authorisation for this product on 23 March 2015.
II QUALITY ASPECTS

II.1 Introduction
The product is a white to off-white, oil in water, homogenous cream, manufactured from conventional pharmaceutical excipients, using a standard manufacturing process.

Each gram contains 20 mg fusidic acid and 1 mg betamethasone as 1.214 mg betamethasone valerate. The excipients present are macrogol cetostearyl ether, cetostearyl alcohol, chlorocresol, liquid paraffin, sodium dihydrogen phosphate-dihydrate, white-soft paraffin, all-rac-α-tocopherol, sodium hydroxide and purified water.

All excipients comply with their European Pharmacopoeia monographs. 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.

The cream is packaged in aluminium tubes of 5, 15, 30 or 60 grams, closed with a polyethylene (PE) screw cap.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Fusidic acid
Chemical name(s): Ent-(17z)-16α-(acetoxy)-3β, 11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10a-cholesta-17(20),24-dien-21-oic acid hemihydrate.

Structure:

Molecular formula: C_{31}H_{48}O_{6}\cdot\frac{1}{2}H_2O
Molecular weight: 525.7 g/mol
Appearance: white or almost white crystalline powder.
Solubility: It is practically insoluble in water, and freely soluble in alcohol.

Fusidic 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 and Healthcare (EDQM) Certificate of Suitability.

**INN: Betamethasone valerate**
Chemical name(s): 9α-Fluoro-11β, 17, 21-trihydroxy-16β-methylpregna-1,4-dien-3,20-dione-17-valerate;
Pregna-1,4-diene-3,20-dione,9-fluoro-11,21-dihydroxy-16-methyl,17-[(1-oxopentyl)oxy]-(11β, 16β) and
9-fluoro-11β,21-dihydroxy-16β -methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate.

Structure:

![Structure](image)

Molecular formula: \( \text{C}_{27}\text{H}_{37}\text{FO}_6 \)
Molecular weight: 476.58 g/mol
Appearance: White or almost white crystalline or microcrystalline powder.
Solubility: It is practically insoluble in water, soluble in ethanol, freely soluble in acetone, methylene chloride and chloroform and slightly soluble in benzene and ether.

Betamethasone valerate is the subject of a European Pharmacopoeia monograph.

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

**II.3 Medicinal Product**
**Pharmaceutical development**
The aim of the development programme was to produce a topical semi-solid preparation that can be used interchangeably with the innovator product, Fucibet 2%/0.1% cream (Leo Laboratories Ltd).

The physicochemical properties of the proposed product versus the reference product sourced from different Member States have shown that the products are highly comparable, with a high degree of pharmaceutical equivalence. The quality attributes investigated and compared included qualitative and quantitative composition, impurity profile, pH, rheological properties, specific gravity, globule size, and particle size and polymorphic form of the active substances.
**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. Process validation data on three commercial scale batches have been provided. The results are satisfactory.

**Finished Product Specification**
The finished product specification, based on the B.P. monographs for fusidic acid cream and betamethasone cream and Ph. Eur. Requirements for topical semi-solid products, is acceptable.

The test methods have been adequately described and validated and batch data 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 30 months for product stored in unopened tubes when the storage precaution ‘Do not store above 30°C’ is applied. Once the tube is opened the product should be used within 6 months.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
The grant of a Marketing Authorisation is recommended.
III NON-CLINICAL ASPECTS

III.1 Introduction
This hybrid application has been submitted in accordance with Article 10.3 of Directive 2001/83/EC, as amended.

As the pharmacodynamic, pharmacokinetic and toxicological properties of fusidic acid and betamethasone valerate are well known, no new non-clinical data have been submitted and none are required. An overview based on literature review is, thus, appropriate.

The Marketing Authorisation Holder’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology
No new data have been submitted and none are required.

III.3 Pharmacokinetics
No new data have been submitted and none are required.

III.4 Toxicology
No new data have been submitted and none are required.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for substitution with reference product, increased in exposure to the environment is anticipated. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.
IV CLINICAL ASPECTS

IV.1 Introduction

Xemacort 20 mg/g + 1 mg/g cream is indicated for the treatment of eczematous dermatoses including atopic eczema, infantile eczema (children of 1 year and over), discoid eczema, stasis eczema, contact eczema and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected.

The product is a topical combination for dermatological use and contains two active substances, fusidic acid and betamethasone valerate. Both active substances are well-established for topical use as single agents and in combination. Fusidic acid is a broad-spectrum antibiotic used in the treatment of bacterial skin infections and betamethasone is a corticosteroid used in inflammatory skin conditions, including eczema.

No new efficacy data were submitted. The data supporting this application consisted of pharmacodynamic studies and local in vitro performance studies only, since these studies were supported by extensive evidence of a high degree of pharmaceutical equivalence.

In support of this application, the Marketing Authorisation Holder has performed the following test to show therapeutic equivalence between the test and reference products for the corticosteroid (betamethasone) component:

- A Phase I pharmacodynamic study to measure the blanching response of the corticosteroid (betamethasone) component of the test product Betamethasone valerate 0.1% Fusidic acid 2% cream versus the reference product Fucibet 0.1%/2% cream (Leo Laboratories Ltd) in healthy volunteers. The study was conducted according to the principles of Good Clinical Practice (GCP).

The Marketing Authorisation Holder has provided the following data package to predict therapeutic equivalence between test and reference products for the antibiotic (fusidic acid) component:

- Comprehensive evidence to show an exceptionally high degree of pharmaceutical equivalence between test and reference product in critical attributes relevant to clinical efficacy and safety of the antibiotic component of the cream

- Three in-vitro studies, comparing the penetration through skin and pharmacodynamic behaviour (anti-microbial activity) of the antibiotic (fusidic acid) component of the test product Betamethasone valerate 0.1% Fusidic acid 2% cream versus the reference product Fucibet 0.1%/2% cream (Leo Laboratories Ltd) in skin samples:
  - In vitro skin permeation study
  - In vitro skin infection study
  - In vitro release (synthetic membrane) study

The Marketing Authorisation Holder’s clinical overview has been written by an appropriately qualified person and is considered acceptable.
IV.2 Pharmacokinetics

There are no data which define the pharmacokinetics of fusidic acid/betamethasone valerate cream, following topical administration in man. However, it is known that 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.

Betamethasone is absorbed following topical administration. The degree of absorption is dependent on various factors including skin condition and site of application. Betamethasone is metabolised largely in the liver but also to a limited extent in the kidneys, and the inactive metabolites are excreted with the urine.

IV.3 Pharmacodynamics

The below study was submitted to demonstrate the therapeutic equivalence of betamethasone (corticosteroid) component of the test product (Xemacort 20mg/g +1mg/g cream) to the reference product (Fucibet 0.1%/2% cream).

A Phase I pharmacodynamic study to measure the blanching response of the corticosteroid (betamethasone) component of the test product Betamethasone valerate 0.1% Fusidic acid 2% cream versus the reference product Fucibet 0.1%/2% cream (Leo Laboratories Ltd) in healthy volunteers.

The study was a two-part (Part A and Part B) open-label, randomised, single-centre study conducted in healthy volunteers to investigate therapeutic equivalence of the steroid component in this product compared with the reference product Fucibet 0.1%/2% cream (Leo Laboratories Ltd) in male and female volunteers with healthy skin.

Part A: The objective of the dose-duration evaluation was to determine the ED₅₀ (effective dose to achieve 50% of the maximal response) for the reference product, Fucibet 0.1%/2% cream (Leo Laboratories Ltd). The estimated ED₅₀ was used to determine the correct dose-duration (in the linear portion of the dose-response curve) for the pivotal clinical pharmacodynamic study.

Part B: The objective of the pivotal therapeutic equivalence evaluation was to assess the pharmacodynamic readout of skin blanching following single topical application of test and reference products, recognised as a valid surrogate for therapeutic equivalence demonstration for topical dermatological corticosteroids.

Methodology

The test and reference products were applied to areas of the ventral forearm, de-marcated using a randomly assigned template; two control regions were also assessed. Chromametry was used to assess the vasoconstrictor response to a single topical application of cream applied for two dose durations (D₁ and D₂) in the linear part of the dose-response, defined in Part A. Chromametry assessment was conducted at time intervals before application (baseline), immediately following cream removal (0hour) and at subsequent times up to 24 hours post cream removal. Chromametric values (a-values) for each time point were baseline-adjusted and control site-corrected.
The primary efficacy variable for the pivotal clinical pharmacodynamic study was the area under the curve for ED<sub>50</sub> from 0 to 24 hours (AUEC<sub>0-24</sub>). The ratio of individual subject mean AUEC<sub>0-24</sub> values for the two dose durations were determined and only those subjects who demonstrated a D<sub>2</sub>/D<sub>1</sub> ratio of ≥ 1.25 were deemed to be detectors and used in the assessment of therapeutic equivalence.

The 90% confidence interval for the test/reference (T/R) ratio of mean AUEC<sub>0-24</sub> values was calculated for detectors only using Locke’s method (according to FDA guidance). The therapeutic equivalence margin was defined as 80-125% for the 90% confidence interval.

Data analysis revealed a 90% confidence interval of 90.29-117.25%, which was within the pre-specified margins of acceptance. The test and reference products were, therefore, concluded to be therapeutically equivalent with respect to the betamethasone component.

### IV.4 Clinical efficacy
Pharmacodynamic studies and local in vitro performance studies were submitted in lieu of clinical therapeutic equivalence studies.

**Betamethasone:**
The validated clinical pharmacodynamic skin blanching study was provided by the Marketing Authorisation Holder to demonstrate therapeutic equivalence for the betamethasone component between this product and reference product (discussed above).

**Fusidic acid:**
*In vitro skin permeation study*
The Marketing Authorisation Holder supplied a study to compare the permeation of test and reference fusidic acid/betamethasone cream in excised human donor skin samples mounted in diffusion cells. The protocol employed was in line with the Guideline on the Quality of Transdermal Patches EMA/CHMP/QWP/911254/2011, and international standards.

The skin samples comprised stratum corneum and epidermal layers only and did not include the dermal layer. Although the stratum corneum is frequently compromised in eczematous conditions, its presence in this assay adds rather than detracts from the discriminatory potential of the assay. Fusidic acid was quantified in the cutaneous layers and also in the receptor fluid as a measure of drug permeation through skin.

Statistical analysis, where the null hypothesis was rejected when the 90% confidence intervals were within an acceptable margin of difference, 80 – 125%, showed that test and reference products were equivalent with respect to permeation and penetration.
Inter-batch and inter-product comparisons of fusidic acid permeation in human skin

Although the assay provided limited quantitative information, given the expected low level of penetration of fusidic acid and consequential variability, from a qualitative perspective the assay provides reassurance that there is a similarly low degree of fusidic acid penetration through the stratum corneum for the proposed and innovator products and from which a similarly low level of systemic absorption can be reasonably inferred. The assay was relevant and important from a safety perspective.

In vitro skin infection study
A study was supplied in which excised skin samples (comprised of stratum corneum and epidermis) from human donors were exposed 

\textit{in vivo} to strains of \textit{Staphylococcus aureus}.

Like the skin permeation study, it was considered that the dermal layer would not add to the discriminatory potential of the assay to identify formulation differences. Post inoculation with bacteria, skin samples were exposed to test and reference products.

Adenosine triphosphate (ATP) luminescence was used as a biomarker for bacterial cell viability and, therefore, bacterial cell count. Although infected skin containing the epidermal layer was incubated with the test and reference products, the analysis was restricted to ATP recovery from the stratum corneum, the rationale being that the residual ATP present in the viable epidermal and dermal layers would interfere with the ATP assay for viable bacteria. ATP recovery, therefore, had to be restricted to a non-viable matrix – the stratum corneum.

Controls included infected and non-infected skin exposed to vehicle.
Statistical analysis, where the null hypothesis was rejected when the 90% confidence intervals were within an acceptable margin of difference, 80 – 125%, showed that test and reference products were equivalent with respect to antimicrobial performance under relevant conditions.

### Antimicrobial activity comparisons of test versus reference products

<table>
<thead>
<tr>
<th></th>
<th>Fucibet UK batch</th>
<th>Goa batches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-infected control</td>
<td>99.1</td>
</tr>
<tr>
<td></td>
<td>Infected control</td>
<td>190.0</td>
</tr>
<tr>
<td></td>
<td>Goa batches</td>
<td>104.9</td>
</tr>
<tr>
<td></td>
<td>Non-infected control</td>
<td>94.5</td>
</tr>
<tr>
<td></td>
<td>Infected control</td>
<td>181.1</td>
</tr>
<tr>
<td></td>
<td>Fucibet UK batch</td>
<td>95.3</td>
</tr>
</tbody>
</table>

Extrapolation of anti-microbial activity from an *ex vivo* study to an authentic clinical context was accepted, in this specific case, because the data provide important qualitative information on anti-bacterial action in the complex environment of the skin.

**In vitro release (synthetic membrane) study**

This study measured rate of release of active substance from vehicle across a synthetic membrane and, from this, inferences regarding partitioning and diffusion across a physical barrier could be made. The study was conducted in accordance with the Food and Drug Administration (FDA) *Scale-Up and Post-approval Changes (SUPAC)* guidance, using a two-stage procedure, with a statistical analysis modified to allow for the two-stage nature of the study. In accordance with SUPAC guidance, the pre-specified acceptance limit for equivalence demonstration was for the 90% confidence interval to lie within a margin of 75 – 133%.

Equivalence was demonstrated for pooled batches of test and reference products:

**Comparisons between pooled batches of the test and reference products for rate of release of fusidic acid**

<table>
<thead>
<tr>
<th>Fusidic acid</th>
<th>Goa cream (PT209, PT210, PT211 T=0)</th>
<th>Goa cream (PT209, PT210, PT211 T=6 months)</th>
<th>77.67 to 98.40</th>
<th>Sameness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fucibet (batches 1, 2 and 3)</td>
<td>100.30 to 125.16</td>
<td>Sameness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fucibet (batches 1, 2 and 3)</td>
<td>85.41 to 110.60</td>
<td>Sameness</td>
</tr>
</tbody>
</table>

Equivalence was also demonstrated for batches of test and reference products that represented extremes in terms of rate of release in the first stage analysis.

**Comparisons between extreme batches of test and reference products for rate of release of fusidic acid**

<table>
<thead>
<tr>
<th>Fusidic acid</th>
<th>Fucibet® Cream UK Batch 3</th>
<th>Goa Cream (PT211) T=6 months</th>
<th>85.43 to 120.10</th>
<th>Sameness</th>
</tr>
</thead>
</table>
Equivalence was demonstrated in accordance with SUPAC guidance, although there are no clinical data to validate that 75 – 133% are acceptable limits for an in vitro release testing study. The results of this study, taken together with results from the in vitro skin permeation and skin infection studies, and the very high degree of pharmaceutical equivalence between test and reference products, were considered sufficient to grant a marketing authorisation.

**Conclusion**
Evidence for robust pharmaceutical equivalence that included a high degree of overall microstructural similarity between test and reference products was provided. It was within this context that the three in vitro studies could be considered as supportive of an overall conclusion of therapeutic equivalence for the fusidic acid component, such that clinical interchangeability could be inferred between the test (Xemacort 20 mg/g +1 g/g cream) and reference (Fucibet 0.1%/2% cream) products. Therefore, the therapeutic equivalence waiver was acceptable.

**IV.5 Clinical Safety**
There were no local tolerance issues recorded during the study and, in light of the longstanding history of use of the originator product Fucibet 0.1%/2% cream, a local tolerance study involving repeated application of test product is considered unnecessary given that strict pharmaceutical equivalence with Fucibet 0.1%/2% cream has been shown.

No new or unexpected safety issues were raised during the clinical study.

**IV.6 Risk Management Plan (RMP)**
The Marketing Authorisation Holder 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 Xemacort 20 mg/g + 1 mg/g cream. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains widely used active substances with a well-established safety profiles.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid-induced undesirable effects</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Information about these typical adverse reactions of steroids in sections 4.4., 4.6, 4.8</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity to the preparation</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Contraindications in section 4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypersensitivity listed in section 4.8</td>
<td></td>
</tr>
<tr>
<td>Local skin reactions e.g. contact dermatitis, allergic reactions</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Local skin reactions listed in section 4.8</td>
<td></td>
</tr>
<tr>
<td>Secondary bacterial, fungal or viral infections</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Precaution about possibly masked secondary infections in section 4.4</td>
<td></td>
</tr>
<tr>
<td>Adrenal suppression – long term continuous therapy particularly in children</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Warning to avoid long term continuous therapy, particularly in children, in section 4.4</td>
<td></td>
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<tr>
<td></td>
<td>• Adrenocortical suppression</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures listed in sections 4.8 and 4.9</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>Atrophic changes after prolonged treatment</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Warning about atrophic changes after prolonged treatment in section 4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atrophic changes listed in section 4.8</td>
<td></td>
</tr>
<tr>
<td>Bacterial resistance</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Precaution in section 4.4 about the risk and reports of bacterial resistance</td>
<td></td>
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<tr>
<td>Ocular complications</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Precaution in section 4.4 when applying the product near the eye and the risk of glaucoma</td>
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<tr>
<td></td>
<td>• Glaucoma listed in section 4.8</td>
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<tr>
<td>Use in pregnancy</td>
<td>Proposed text in SmPC:</td>
<td>None proposed.</td>
</tr>
<tr>
<td></td>
<td>• Information about lack of safety data in pregnancy in section 4.6</td>
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</table>
IV.7 Discussion on the clinical aspects

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

Therapeutic equivalence between this product and the reference product (Fucibet 0.1%/2% cream) for the betamethasone component of the cream was considered to have been demonstrated through a clinical pharmacodynamic (skin blanching, vasoconstrictor) study.

A pharmacodynamic assay, suitable as a surrogate for clinical efficacy studies, was not available for the fusidic acid component of the cream. But the Marketing Authorisation Holder has provided physicochemical data that demonstrated an exceptionally high degree of equivalence between this product and the reference product in all critical quality attributes, which together with the three in vitro studies (with respect to antimicrobial activity, drug release and skin penetration) were sufficient to conclude therapeutic equivalence, and clinical interchangeability, in this specific case.

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 patient information leaflet (PIL) was English.

The PIL 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 concerns have been identified. Extensive clinical experience with fusidic acid and betamethasone valerate is considered to have demonstrated the therapeutic value of the compound. Clinical interchangeability between this product and the reference product has been demonstrated for both the betamethasone and fusidic acid components.

Therapeutic equivalence for the betamethasone component was demonstrated by the fully validated clinical pharmacodynamic (skin blanching) study. With respect to the fusidic acid component, in the unusual circumstance of an exceptionally high degree of pharmaceutical equivalence, the in vitro studies submitted were sufficient to complete the package of critical performance attributes from which, collectively, therapeutic equivalence could be inferred, in this specific case.

The benefit/risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

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

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