FUCIBET ® LIPID CREAM
(FUSIDIC ACID 2%, BETAMETHASONE 0.1%)

PL 00043/0218

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted LEO Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Fucibet ® Lipid Cream (PL 00043/0218) on 6th February 2007. This is a prescription-only medicine (POM) used for the treatment of a variety of skin conditions.

Fucibet ® Lipid Cream contains the active ingredients fusidic acid 2% (20mg/g), which belongs to a group of medicines called antibiotics, and betamethasone 0.1% (1mg/g), as betamethasone valerate, which belongs to a group of medicines called steroids. Fucibet ® Lipid Cream works by reducing swelling, itchiness and redness, and by killing the bacteria that cause the skin infection.

The cream is used to treat inflamed skin conditions such as eczema and dermatitis which are also infected with bacteria. It should not be used for those skin conditions caused only by bacteria, e.g. boils and spots, by viruses, e.g. cold sores, and by fungi, e.g. athelete's foot. It should also not be used to treat acne rosacea or a type of dermatitis with spots around the mouth and chin.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Fucibet ® Lipid Cream outweigh the risk, hence a Marketing Authorisation has been granted.

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PL 00043/0218

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted LEO Laboratories Limited a Marketing Authorisation (MA) for the medicinal product Fucibet ® Lipid Cream (PL 00043/0218) on 6th February 2007. The product is a prescription-only medicine (POM) indicated for the treatment of a variety of inflammatory skin conditions such as eczema and dermatitis which are also infected with bacteria.

This is a national abridged standard application for Fucibet ® Lipid Cream, containing Fusidic Acid 2% w/w and Betamethasone 0.1% w/w (as the valerate), submitted under article 8.3 of Directive 2001/83/EC, as amended - a complete application of known active substances, as a line extension to Fucibet ® Cream, PL 00043/0091, granted 27 October 1983. The proposed application contains the same actives in the same concentrations (fusidic acid 2% (20mg/g) and betamethasone 0.1% (1mg/g), as the valerate) as the licensed product, but in a new formulation.

Fucibet ® Lipid Cream is a combination product containing two actives: the antibiotic fusidic acid - active against *Staphylococcus aureus* and the anti-inflammatory steroid betamethasone-17-valerate. It is used for the cutaneous treatment of eczematous dermatoses including atopic eczema, discoid eczema, stasis eczema and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected.

The application is supported by *in vitro* skin permeability studies and a single Phase III efficacy study to show therapeutic equivalence between Fucibet ® Lipid Cream and Fucibet ® Cream. These studies are discussed in the Pre-clinical and Clinical Assessment sections of the report.

PHARMACEUTICAL ASSESSMENT

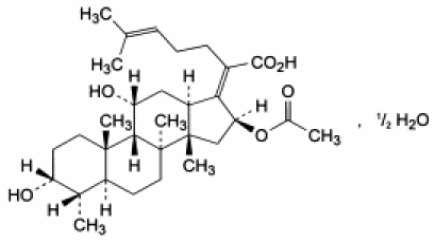
ACTIVE SUBSTANCE

Fusidic Acid

Nomenclature:

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 weight:	525.7
CAS No:	6990-06-3

Physical form:	A white or almost white crystalline powder
Solubility:	Freely soluble in alcohol, practically insoluble in water, and insoluble in oil-in-water formulation of the drug product

The active substance, fusidic acid, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the materials used are not derived from animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided based on the European Pharmacopeia specification. Satisfactory details have been provided for the compendial and non-compendial test methods.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Active fusidic acid is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging components. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for fusidic acid stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 12 months at a storage condition of between 2-8°C, when stored in the proposed packaging.

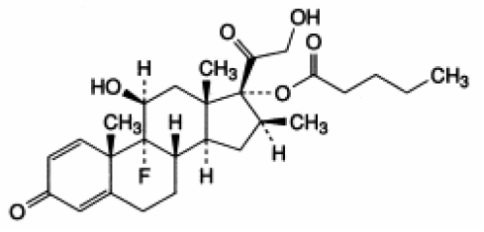
ACTIVE SUBSTANCE

Betamethasone valerate

Nomenclature:

INN:	Betamethasone valerate
Chemical name:	9-fluoro-11β,21-dihydroxy-16β -methyl-3,20- dioxopregna-1,4-dien-17-yl pentanoate,

Structure:



Molecular formula:	$C_{27}H_{37}O_6$
Molecular weight:	476.6
CAS No:	2152-44-5

Physical form:	A white or almost white crystalline powder, odourless
Solubility:	Practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in ethanol, and insoluble in oil-in-water formulation of the drug product

The active substance, betamethasone valerate, is the subject of a Ph. Eur. monograph.

All aspects of the manufacture and control of betamethasone valerate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of betamethasone valerate for inclusion in this medicinal product.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the drug substance and supports a retest period of 5 years at a storage condition of below 25°C, when stored in the proposed packaging.

DRUG PRODUCT

Description & Composition

Fucibet Lipid Cream is a white, highly viscous oil-in-water emulsion cream containing 60% oily phase. The active substances, fusidic acid and betamethasone valerate, are suspended as micronized materials in the formulation.

Other ingredients consist of pharmaceutical excipients, namely steareth-21 (macrogol (21) stearyl ether), cetostearyl alcohol, white soft paraffin, liquid paraffin, hypromellose, citric acid monohydrate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, potassium sorbate, and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Steareth-21 which complies with a satisfactory in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is betamethasone valerate. A Certificate of Suitability has been provided by the supplier of betamethasone valerate stating that the betamethasone valerate they provide meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 reference standards used.

Container Closure System

The cream is filled into aluminium tubes with re-closable polyethylene screw caps, provided with spike. The inside of the tube is lacquered with a suitable material. The tube is sealed with a membrane, which makes it tamper evident. Prior to use, the membrane is pierced by means of the spike in the cap. The tubes are packaged with

the PIL (Patient Information Leaflet) into cardboard outer cartons. There are four pack sizes available, 5g, 15g, 30g and 60g, although the MA holder has stated that not all pack sizes will be marketed.

All primary product packaging, including the tube lacquer, complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the unopened tube. Once the tube has been opened, the shelf-life is 3 months. This is satisfactory. The storage instructions are ‘Store in the original container’ and ‘Do not store above 25°C’.

Bioequivalence Study

There was no bioequivalence study carried out to support this application. Instead, clinical data are provided to demonstrate therapeutic equivalence to the reference product, in line with the Notes for Guidance ‘on the clinical requirements for locally applied, locally acting products containing known constituents’, CPMP/EWP/239/95 Final. The clinical study and data are discussed in the Clinical Assessment section.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

BACKGROUND

This is an abridged standard national application for Fucibet Lipid Cream, submitted by LEO Laboratories Limited under Article 8.3, known active substance, of Council Directive 2001/83/EC, as amended. It is a line extension of Fucibet Cream (PL 00043/0091) and contains the same active ingredients, fusidic acid 20mg/g and betamethasone 1mg/g (as the valerate).

The product is a fixed combination of an oil-in-water cream containing the well-established active ingredients, the antibiotic fusidic acid 20mg/g, and the corticosteroid betamethasone 1mg/g (as the valerate). It differs from the existing product in containing lipid-based excipients to provide a more greasy formulation. It is intended for the cutaneous treatment of eczematous dermatoses, including atopic eczema, discoid eczema, stasis eczema and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected. It is recommended that a small quantity be applied to the affected area twice daily for a maximum of fourteen days per course of treatment.

The non-clinical programme consisted of a local tolerance study in rabbits and studies to investigate the potential for altered cutaneous absorption resulting from the new excipients; the non-clinical overview concentrates on these.

Good Laboratory Practice (GLP) aspects

Two *in vitro* studies on skin penetration were conducted to reasonable standards. The local tolerance study in rabbits was GLP-compliant.

PHARMACODYNAMICS / PHARMACOKINETICS / TOXICOLOGY

The actions of fusidic acid and betamethasone have been characterised in previous submissions. The existing formulation has been in use world-wide since 1983. The absence of new pharmacology and pharmacodynamic studies was justified on this basis.

Fusidic acid is a member of the fucidane group of naturally-occurring antibiotics that exerts its action by blocking the protein synthesis of bacteria. Betamethasone, as a topical corticosteroid, has anti-inflammatory, anti-pruritic, and vasoconstrictive actions but the exact mechanisms of these actions are unknown.

Pharmacokinetics

Two *in vitro* studies have been performed to investigate the possibility of altered percutaneous absorption resulting from the new excipients:

- A study in intact pig ear skin
- A study in both intact and barrier-impaired pig skin simulating atopic dermatitis

The study in intact pig ear skin demonstrated a four-fold and a three-fold increase in the penetration of fusidic acid and betamethasone, respectively, from the lipid-based cream compared with the existing product. In the study using intact and barrier-impaired skin, the intact skin also showed greater penetration from the new formulation but there was no significant difference between the two creams for the barrier-impaired skin. For both formulations, the penetration through barrier-impaired skin was significantly greater than through intact skin.

Toxicology

Six male rabbits were treated once daily for three weeks with 100mg of Fucibet Lipid Cream and vehicle cream. The treated area was not occluded. The skin was examined daily for erythematous reactions and the skin-fold thickness was measured once weekly. At termination, the skin was examined histopathologically.

Both the vehicle and drug-containing lipid creams were tolerated. Slight effects on skin thickening were seen generally. Those with the vehicle cream were greater than with the drug-containing cream; this is suggestive of a mild irritant effect of the vehicle that was negligible when betamethasone was present in the formulation.

It was concluded that repeated topical non-occlusive treatment of rabbits once daily for three weeks induced minimal skin irritation that was ascribed to the vehicle.

It is well known that systemic absorption of significant amounts of corticosteroids can cause suppression of the hypothalamic-pituitary-adrenal axis. It is argued that the absorption from the new Fucibet Lipid Cream is not likely to differ from that of the existing formulation in barrier-impaired skin although higher absorption is possible through intact skin. Since treatment will be discontinued when the skin heals and is recommended for two weeks only, it is concluded that the risk of systemic toxicity is low.

Assessor's comment
The conclusion that the amount of percutaneously absorbed drugs from the lipid-based cream is unlikely to differ from the currently marketed product Fucibet Cream in barrier-impaired skin is supported by the data. The argument regarding the likelihood of systemic toxicity being low is accepted and there is considerable clinical experience with Fucibet Cream.

EXCIPIENTS / IMPURITIES / RESIDUAL SOLVENTS

The excipients are all commonly used in topical formulations and comply with the European Pharmacopoeia. The related substances in fusidic acid have been shown to have acute toxicity profiles similar to that of fusidic acid. The impurities and residual solvents in both drug substances are present in amounts compliant with the relevant ICH Notes for Guidance.

ENVIRONMENTAL RISK ASSESSMENT

The applicant has calculated Predicted Environmental Concentrations (PEC) in surface water for both active ingredients that have triggered a Phase II environmental effect analysis for both actives, although the assessor felt that only fusidic acid required further analysis. The further analyses were conducted and the final risk

quotients for both drugs appear reasonable; it is concluded that there is no risk to the environment.

There is a risk of some bioaccumulation of betamethasone but not fusidic acid.

Assessor's comment
The conclusion is considered reasonable and the assessor concurs that there is no evidence of a risk to the environment from the new formulation. It is also the case that the new formulation is likely to replace the currently marketed cream for some patients rather than adding to the overall quantity marketed.

NONCLINICAL OVERVIEW

A preclinical expert report has been written by a suitably qualified person and is satisfactory. An appropriate CV has been provided for the expert.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Sections 4.6 and 5.3 of the SmPC are consistent with those for Fucibet Cream. The final SmPC is satisfactory.

CONCLUSION

This application has not revealed any evidence of untoward toxicity with Fucibet Lipid Cream, beyond the known effects of betamethasone and fusidic acid, and adequate warnings are proposed. There is no objection to the grant of a licence from a pre-clinical point of view. A Marketing Authorisation may be granted.

CLINICAL ASSESSMENT

I BACKGROUND

This proposed line-extension, Fucibet Lipid Cream, contains the same actives as Fucibet Cream, in the same concentrations, but in a new formulation. The new vehicle has been developed to offer the atopic dermatitis (AD) patient effective treatment of infected dermatitis but with improved skin hydration.

Combinations of topical corticosteroids and antibiotics have become established treatments for clinically infected AD and Fucibet Cream has been used for more than 20 years. This water-based preparation is well-absorbed, however, because the skin in AD varies in terms of dryness during the course of the disease, Fucibet Cream may not always be suitable. Fucibet Lipid Cream is a more lipophilic preparation and therefore more suitable for a dry skin condition. As the symptoms of AD and dryness of the skin vary between patients and within the same patient on different areas of skin, patients benefit from a range of preparations depending on their status at the time.

The application is supported by *in vitro* skin permeability studies and a single Phase III efficacy study to show therapeutic equivalence between Fucibet Lipid Cream and Fucibet Cream. The *in vitro* work is discussed in the Pre-clinical Assessment section.

I.1 GCP ASPECTS

A single Phase III clinical study (Study A) was conducted and performed in accordance with GCP.

II INDICATIONS

Fucibet Lipid Cream is indicated for the treatment of eczematous dermatoses including atopic eczema, discoid eczema, stasis eczema and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected.

III CLINICAL PHARMACOLOGY

Pharmacokinetics

No new clinical pharmacology work has been conducted. However, pre-clinical work looking at the absorption of the actives in Fucibet Lipid Cream and Fucibet Cream across intact and stripped skin from pig cadavers was carried out and has been reviewed in the Pre-clinical Assessment section.

Absorption

It is accepted that disruption of the barrier function of the stratum corneum is an essential aetiological factor in patients with AD; therefore the stripped skin model is considered of more relevance due to properties similar to the skin of AD patients. *In vitro* permeation of Fucibet Lipid Cream through intact and barrier-impaired (tape-stripped) skin was compared. The model used full-thickness skin from cadaver pig ears. The creams were applied twice a day and diffusion cells were applied to the skin, the treatments were applied to the skin and the fusidic acid and betamethasone-17-valerate were recovered from the receptor medium on the other side.

The findings are summarised in Table 1 below. For intact skin, absorption of Fucibet Lipid Cream was greater than for the aqueous based Fucibet Cream – but this difference was not statistically significant. Permeation through stripped skin was, as would be anticipated, much higher for both preparations but there was no statistically significant difference between them. The applicant therefore claims that, using the more clinically relevant model of stripped skin, similar absorption of the actives would be expected for Fucibet Lipid Cream compared to the licensed Fucibet Cream.

Table 1: Comparison of permeation of fusidic acid and betamethasone-17-valerate through intact and barrier-impaired skin for Fucibet Cream and Fucibet Lipid Cream

Mean total amount permeated (µg/cm2)				
	Intact skin		Stripped skin	
	Fusidic acid	Betamethasone -17-valerate	Fusidic acid	Betamethasone-17-valerate
Fucibet Cream	2	5	22	19
Fucibet Lipid Cream	6	8	24	17

Assessor's overall conclusions on pharmacokinetics

The dermal absorption of fusidic acid and betamethasone has not been measured. However, *in vitro* studies do not suggest a clinically relevant greater skin permeation with Fucibet Lipid Cream compared to Fucibet Cream, even in barrier-impaired skin simulating AD. Therefore, a higher absorption of Fucibet Lipid Cream compared to Fucibet Cream is not anticipated. The argument regarding the likelihood of systemic toxicity being low is therefore accepted, and there is considerable clinical experience with Fucibet Cream.

Pharmacodynamics

ATC Code: D07C C01 Corticosteroids, potent, combination with antibiotic

Mechanism of action

Fusidic acid has topical bactericidal activity against *Staphyloccus aureus*, a major pathogen in infected AD. The mechanism of action of corticosteroids in AD is not fully understood, but efficacy is well-established.

Primary pharmacodynamics

Fusidic acid: This is a member of the fucidane group of naturally occurring antibiotics and blocks protein synthesis in bacteria whose cell-membrane is permeable to fusidic acid. It is active against a wide range of gram-positive organisms and gram-negative *cocci*, and is particularly effective against *staphylococci*. It is not inactivated by penicillinase and is, therefore, fully effective against penicillin-resistant *staphylococci*.

Betmethasone: This is effective in AD because of an anti-inflammatory, anti-pruritic and vasoconstrictive action and the physiological, pharmacological, and clinical effects are well-known, although the exact mechanism of action is unknown. It is a

corticosteroid in which the chemical structure has been changed to accentuate the anti-inflammatory properties and to depress the other properties of the corticosteroids. It has both local anti-inflammatory and immunosuppressive activity and inhibits the adherence of neutrophils and monocytes/macrophages to the capillary and endothelial cells within the inflamed area. The drug blocks the effect of the macrophage migration inhibitor factor and decreases the activation of plasminogen to plasmin. Finally, by inhibition of phospholipase A2 activity, via formation of lipocortin, betamethasone reduces the formation of prostaglandins and leukotrienes in local tissue. Betamethasone is regarded as a medium potency corticosteroid.

Secondary pharmacodynamics

Both actives are well known and no further studies have been conducted.

Assessor's overall conclusions on pharmacodynamics

No new studies have been conducted and none are required..

IV CLINICAL EFFICACY

A single clinical Phase III study (Study A) was performed comparing Fucibet Lipid Cream with Fucibet Cream and Fucibet Lipid Cream Vehicle in clinically infected atopic dermatitis.

Methods

The study was a multi-centre, double-blind, randomised study to compare the efficacy and safety of Fucibet Lipid Cream with Fucibet Cream and Fucibet Lipid Cream Vehicle applied twice daily for two weeks in patients with clinically infected AD. The study was conducted according to GCP.

- **Study Participants**

All patients assessed, except one, had clinically diagnosed infected AD with a minimum score of 1 (slight involvement) for each of the following signs: erythema, oedema/papules, oozing/crusting, and excoriation, and a target area measuring at least 4 x 4cm.

- **Treatments**

Patients were randomised to receive the three treatments and each received 3 tubes of 30g at visits 1 and 2. Care was taken to maintain the blind for both patients and investigator. Patients were instructed to apply the treatment as a thin layer to all the affected skin lesions, rubbing it in gently. There were no specific recommendations regarding the quantity of cream to be used. Compliance was monitored.

- **Objectives**

The primary objective was to show non-inferiority of Fucibet Lipid Cream to Fucibet Cream.

The secondary objective was to show superiority of Fucibet Lipid Cream to Fucibet Lipid Cream Vehicle.

- **Outcomes/endpoints**

A target area of AD on the trunk or limbs was chosen to make the baseline assessment measures of severity; body surface area of AD was not included. The target area was chosen as representative of the patients' affected skin.

The total severity score (TSS) measured:

a) Erythema
b) Oedema/population
c) Oozing/crusting
d) Excoriation

and each item was scored on the 4-point scale below, giving a score range of 0-12:

0 = absent
1 = slight involvement
2 = moderate involvement
3 = severe involvement

In addition, the patient and investigator were asked to evaluate the overall response to therapy; this measurement took into account the efficacy of the treatment with respect to all areas of skin affected by AD. These were simple six-point ordinal scales evaluating any change relative to baseline.

A total severity score, based on the above signs, was evaluated at all visits. The investigator's and the patient's overall efficacy assessments relative to baseline were evaluated during the study. Swabs for bacteriological culture were taken at baseline and also at subsequent visit(s), if clinically infected lesions persisted.

- **Sample size**

Out of a total of 630 patients enrolled in the study, 629 were included in the analyses.

- **Randomisation**

Patients were randomised in the ratio 3:3:1 Fucibet Lipid Cream: Fucibet Cream: Fucibet Lipid Cream Vehicle, respectively.

- **Statistical methods**

The percentage reduction in total severity score was used as the measure of non-inferiority of Fucibet Lipid Cream compared to Fucibet Cream. A lower limit of difference of 10% between the two treatments was chosen as the non-inferiority margin. In the two active treatment groups the actual mean TSS changed from 8.4 to 1.5 and 8.2 to 1.6, respectively. In practice this means that the -10% difference between the two reductions in TSS (as the limit for non-inferiority) are less than 1 point on the 0-12 scale. This difference in response would have very little significance for the patient with regard to lack of improvement in symptoms. In actual fact, the lower 95% CI (Confidence Interval) was -3.83% difference between the two treatment groups responses, equating to -0.2 difference in TSS in favour of Fucibet Cream.

The analysis of the primary endpoint was performed on a per protocol (PP) basis, in accordance with ICH recommendations. According to the Note for Guidance on the

Clinical Requirements for locally applied, locally acting products containing known constituents, it is necessary to show that the locally acting product to be approved is therapeutically equivalent to the product already approved with regard to safety and efficacy.

The intention to treat (ITT) analysis set was considered primary for the comparison between Fucibet Lipid Cream and Fucibet Lipid Cream Vehicle.

Results

- **Participant flow**

Of the 630 patients enrolled and randomised, in total, 15 patients were excluded from the PP analysis set.

- **Baseline data**

The patients were well distributed in terms of duration of AD in the treatment groups; approximately 40% 0-5 years duration, 40% 6-10 years duration, and 20% >10 years.

The mean baseline total severity score (possible range 0-12) was 8.2 - 8.3 in each of the treatment groups. Baseline intensity of AD measured on this scale was at least moderate.

Active Treatment Comparison

- **Primary efficacy results**

After two weeks' treatment the mean reduction in TSS in the Fucibet Lipid Cream group was 82.9% and 82.7% in the Fucibet Cream group (see Table 2). The estimated treatment difference between these two groups was 0.23%, and a p-value of <0.001 was obtained with a 1-sided t-test for non-inferiority. These data confirm that Fucibet Lipid Cream is non-inferior to Fucibet Cream.

Table 2: Active comparison: %age reduction in the Total Severity Score (TSS) from Baseline to End-of-Treatment (PP analysis set)

%age reduction in TSS	Fucibet lipid cream (n=274)	Fucibet cream (n=254)	Treatment comparison[1] (ANCOVA) Difference (95%CI)[2] p-value[3]
Mean	82.9	82.7	0.23% (-3.83;4.30)
Median	90.9	90.0	p<0.001
SD	24.5	24.7	
Minimum	-57.1	-57.1	
Maximum	100.0	100.0	
Number	274	254	

1. ANCOVA, including baseline TSS as a covariate and centre and treatment as design variables
2. two-sided 95% CI
3. One-sided t-test for inferiority

- **Secondary efficacy endpoints**

The comparison between Fucibet Lipid Cream and Fucibet Cream was also analysed in the ITT data-set. The conclusion was the same as for the PP data-set; the difference in percentage reduction in TSS was 2.3% (95% CI -2.13; 6.74).

Fucibet Lipid Cream vs Fucibet Lipid Cream Vehicle comparison

A comparison between Fucibet Lipid Cream and its vehicle was performed. The null hypothesis for this analysis was that the difference in mean TSS reduction was 0%, i.e. that Fucibet Lipid Cream had no additional efficacy over vehicle. For this analysis the ITT data-set was used. The estimated difference between the active and vehicle was 48.3% (95% CI 41.0; 55.7); p <0.001 (see Table 3). It can be concluded, therefore, that there is a significant difference in terms of reduction in TSS between active treatment and vehicle.

Table 3: Vehicle comparison: %age reduction in TSS from Baseline to End-Of-Treatment (ITT analysis set)

%age reduction in TSS	Fucibet lipid cream (n=275)	Fucibet lipid cream vehicle (n=90)	Treatment comparison[1] (ANCOVA) Difference (95%CI)[2] p-value[3]
Mean	82.7	33.0	48.3% (41.0;55.7) p<0.001
Median	90.9	33.3	
SD	25.0	41.4	
Minimum	-57.1	-100.0	
Maximum	100.0	100.0	
Number	275	90	

1. ANCOVA, including baseline TSS as a covariate and centre and treatment as design variables
2. two-sided 95% CI
3. F-test

Additional analyses

The individual severity scores were analysed by treatment groups for weeks 0, 1 and 2. There were no major differences between Fucibet Lipid Cream and Fucibet Cream in terms of percentage change in severity score at the end of treatment. This demonstrates that all components of the TSS (erythema, oedema/population, oozing/crusting, excoriation) were changed in the same direction by both treatments.

Investigators were asked to assess the patients at each on-treatment visit for overall efficacy. Patients who showed 'marked improvement' or were 'completely cleared' were classified as 'responders'. The percentage of responders at the end of treatment was very similar between the two active treatment groups; Fucibet Lipid Cream and Fucibet Cream: 83.5% and 84.0%, respectively. This gave an estimated difference of 0.5% (95% CI -6.8; 5.8).

Patients were asked to make the same assessment of their AD response to treatment. Responders and non-responders were defined in the same way. Percentage responders in the Fucibet Lipid Cream and Fucibet Cream groups at the end of treatment were 82.1% and 84.0%, respectively. This gave an estimated difference of -2.0% (95% CI -

8.4; 4.5). All the secondary analyses supported the primary analysis in that the response of AD to Fucibet Lipid Cream and Fucibet Cream was very similar.

Subgroup analyses

No subgroup analyses were planned but they were performed after the principle analyses to look for any possible large differences between patient sub-groups with respect to efficacy. No difference in response to the two active treatment groups was seen in the sub-groups defined according to age, sex, duration of AD, and baseline severity of AD.

Bacteriological Response

The protocol included patients with a diagnosis of clinically infected AD as evaluated by the treating physician and laboratory swab results were not required prior to including each patient. Bacteriological response did not form part of the primary analysis of non-inferiority. However, the bacteriological response was found to be very similar. The successful bacteriological response in the Fucibet Lipid Cream group was 87.8% and in the Fucibet Cream group 83.2% (ITT analysis set). The difference between treatments was 4.7% (95% CI -2.5; 12.0).

Assessor's overall conclusions on clinical efficacy

Study A met the primary endpoint and showed that Fucibet Lipid Cream is non-inferior to Fucibet Cream in reducing the severity of clinically infected AD. In the treatment of clinically infected AD, both Fucibet Lipid Cream and Fucibet Cream showed significant clinical and antibacterial efficacy, as well as favourable safety and local tolerability profiles. Superiority of Fucibet Lipid Cream to its vehicle was also demonstrated. Physician and patient assessments of overall improvements in severity also supported this conclusion.

V CLINICAL SAFETY

The active ingredients in Fucibet Lipid Cream have been used in the same proportions in Fucibet Cream, which has been licensed and marketed throughout Europe for >20 years. All the components of Fucibet Lipid Cream: active substances and excipients comply with standards in the European Pharmacopoeia. The patients recruited into the efficacy study (Study A) were representative of the target population and the method of application (patients were asked to apply the treatment to the affected area in a thin layer and rub gently) is similar to use outside the clinical trial situation.

Patient exposure

275 patients from Study A were exposed to Fucibet Lipid Cream applied twice daily for two weeks and were included in the safety dataset. The mean duration of exposure was 2.18 weeks, giving a total exposure of 599 treatment weeks. There are no longer-term safety data for Fucibet Cream but there is no anticipated safety concern.

Adverse events

The proportion of patients who experienced any adverse event (AE) was 13.5% in the Fucibet Lipid Cream group, 10.5% in the Fucibet Cream group, and 21.6% in the Fucibet Lipid Cream Vehicle group.

The incidence was therefore similar in the two active treatment groups. Lack of efficacy of the vehicle probably accounts for the symptoms of AD being recorded as AEs.

Although the study was not statistically powered for a comparison of AEs, there was no statistically significant difference in the proportion of patients who experienced AEs (p = 0.28 by Chi-squared analysis). Table 4 summarises the AEs by primary system organ class.

Table 4: AEs by Primary Organ Class – active treatment groups

Primary Organ Class System	Fucibet Lipid Cream (n=272)	Fucibet Cream (n=258)
Eye disorders	3	1
Gastrointestinal disorders	1	9
General disorders and administration site condition	1	1
Immune system disorders	1	0
Infections and infestations	8	5
Injury, poisoning	2	2
Musculoskeletal and connective tissue disorders	1	2
Nervous system disorders	7	5
Psychiatric disorders	1	0
Respiratory and thoracic disorders	5	0
Skin and subcutaneous tissue disorders	10	6
Surgical and medical procedures	1	0
Total number of AEs	41	31
Total number of patients (%)	37 (13.5)	27 (10.5)

AEs were defined as ADRs where the investigator had not excluded a causal relationship, i.e. they were considered ‘possible’, ‘probable’, or ‘not assessable’. All ADRs were within the ‘Skin and subcutaneous disorders’ primary organ class system.

Overall the total number and percentage of patients in the Fucibet Lipid Cream group experiencing an ADR was very low: a total of 7 ADRs were reported in 7 patients (2.6%):

Five were mild - pruritus, urticaria, skin burning sensation (3)
Two were severe - erythema and pruritus

In the Fucibet Lipid Cream Vehicle group there were 15 ADRs:

Five were mild - dry skin, prurigo, skin tightness and skin-burning sensation (2)
four were moderate - skin burning sensation and pruritus (3)
six were severe - contact dermatitis, skin pain, skin burning sensation and pruritus (3)

In the Fucibet Cream group, 4 ADRs were reported in 4 patients (1.6%)

Although the reported incidence of ADRs was lower in the Fucibet Cream group, the applicant comments that the numbers are too low and too similar to conclude that Fucibet Lipid Cream might have a higher incidence of ADRs.

Assessor's comment
The Assessor agrees with the above comment and that the safety profile is acceptable for Fucibet Lipid Cream.

Serious adverse events and deaths

None reported

Post-marketing experience

No new safety concerns have arisen with Fucibet Cream and the Clinical Study indicates that AEs are similar with Fucibet Lipid Cream and, therefore, a similar safety profile is to be expected in clinical practice.

Assessor's overall conclusions on clinical safety

The safety profile of Fucibet Lipid Cream is acceptable in that the incidence of ADRs is low and no clear difference is seen when compared to the marketed Fucibet Cream.

VI EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

VII PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SmPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SmPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

DISCUSSION AND CONCLUSION

Corticosteroids and antibiotics, in combination, have a role in the treatment of clinically infected AD. There is a range of licensed products available, including Fucibet Cream. Fucibet Lipid Cream would be a useful addition to this range of treatments because the more occlusive, ointment-type vehicle is more suited to certain dry skin types in AD patients.

The clinical trial, Study A, has demonstrated that, in patients aged 6 years and over, Fucibet Lipid Cream is non-inferior to Fucibet Cream in terms of reducing the severity of AD. The trial met the pre-defined endpoint of non-inferiority compared to Fucibet Cream. The percentage reduction in AD severity for Fucibet Lipid Cream was 82.9% and the estimated difference in severity reduction compared to Fucibet Cream

was less than 1%. Any true difference in efficacy between Fucibet Lipid Cream and Fucibet Cream is likely to be very small, therefore, and of no clinical significance. Although subgroup analyses were not pre-specified, there were no indications that subgroups of patients may have responded less well to Fucibet Lipid Cream.

The clinical trial, therefore, supports the SmPC for the treatment of clinically infected AD in adults and children from 6 years of age. The safety profile is acceptable in relation to these benefits being similar to that of Fucibet Cream. The incidence of ADRs was less than 3% in the clinical trial and all involved the skin or subcutaneous tissue. Furthermore, the antibacterial activity of Fucibet Lipid Cream was very good in those subjects in whom a bacterial strain was identified. To avoid the emergence of resistant strains (a potential concern with all antibacterial agents if not used correctly) the approved SmPC posology reflects the clinical trial and aims to prevent inappropriate antibacterial prescribing. To this end, it stipulates that treatment be limited to a maximum of two weeks, with twice a day usage.

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support this application. When used as indicated, Fucibet Lipid Cream has a favourable benefit-to-risk ratio. A Marketing Authorisation is, therefore, recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Fucibet ® Lipid 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.

PRECLINICAL

A pre-clinical expert report has been provided by an appropriately qualified consultant. This application has not revealed any evidence of untoward toxicity for Fucibet ® Lipid Cream.

EFFICACY

The clinical study has demonstrated the efficacy of Fucibet ® Lipid Cream and shown it to be therapeutically equivalent to the originally licensed product, Fucibet ® Cream

The clinical study identifies no new safety issues or concerns.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory.

The Marketing Authorisation Holder has provided a commitment to update the Marketing Authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with the active substances fusidic acid and betamethasone valerate as a combination product is considered to have demonstrated the therapeutic value of the drug product. The risk: benefit is, therefore, considered to be positive.

FUCIBET ® LIPID CREAM
(FUSIDIC ACID 2%, BETAMETHASONE 0.1%)

PL 00043/0218

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 17th September 2004

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 28th September 2004

3 Following assessment of the application the MHRA requested further information relating to the clinical dossier and quality dossier on 11th March 2005

4 The applicant responded to the MHRA's requests, providing further information for the clinical sections and the quality sections on 15th July 2005

5 Following assessment of the response the MHRA requested further information relating to the quality sections on 5th May 2006

6 The applicant responded to the MHRA's request, providing further information for the quality sections on 16th November 2006

7 The application was determined on 6th February 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fucibet ® Lipid Cream is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fucibet® Lipid cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fucibet® Lipid cream contains Fusidic acid 2% and Betamethasone 0.1% (as the valerate ester).

Fucibet® Lipid cream also contains methyl parahydroxybenzoate 0.1% and propyl parahydroxybenzoate 0.02%. For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

White Cream

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fucibet® Lipid cream is indicated for the treatment of eczematous dermatoses including atopic eczema, discoid eczema, stasis eczema and seborrhoeic eczema when secondary bacterial infection is confirmed or suspected.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and children aged 6 years and over:

A small quantity should be applied to the affected area twice daily until a satisfactory response is obtained. A single treatment course should not normally exceed 2 weeks. In the more resistant lesions the effect of Fucibet® lipid cream can be enhanced by occlusion with polyethylene film. Overnight occlusion is usually adequate.

4.3 CONTRAINDICATIONS

Known hypersensitivity to the drug substances or to any of the ingredients.
Acne rosacea and perioral dermatitis. Skin lesions of viral, fungal or bacterial origin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Long-term continuous topical therapy should be avoided, particularly in children. Adrenal suppression can occur even without occlusion. Atrophic changes may occur on the face and to a lesser degree in other parts of the body, after prolonged treatment with potent topical steroids. Caution should be exercised if Fucibet® Lipid cream is used near the eye. Glaucoma might result if the preparation enters the eye. Systemic chemotherapy is required if bacterial infection persists.

Bacterial resistance has been reported to occur with the use of fusidic acid applied topically. As with all topical antibiotics, extended or recurrent application may increase the risk of contact sensitisation and the development of antibiotic resistance.

Steroid-antibiotic combinations should not be continued for more than 7 days in the absence of any clinical improvement since in this situation occult extension of the infection may occur due to the masking of the steroid. Similarly, steroids may also mask hypersensitivity reactions.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

None known

4.6 PREGNANCY AND LACTATION

Topical administration of any corticosteroid to pregnant animals can cause abnormalities of foetal development. The relevance of this finding to human beings has not been established; however, topical steroids should not be used extensively in pregnancy, i.e. in large amounts or for prolonged periods

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable

4.8 UNDESIRABLE EFFECTS

Prolonged and intensive treatment with potent corticosteroids may cause local atrophic changes in the skin, including striae, thinning and dilation of superficial blood vessels, particularly when applied to the flexures or when occlusion is employed. As with other topical corticosteroids sufficient systemic absorption to produce hypercorticism can occur with prolonged or extensive use. Children are at particular risk. Hypersensitivity reactions to fusidic acid are rare and Fucibet® Lipid cream does not contain lanolin. However, if signs of hypersensitivity occur, treatment should be withdrawn.

4.9 OVERDOSE

Not applicable

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Fucibet® Lipid 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 *Staphyloccus aureus,* Streptococci, Corynebacteria, Neisseria and certain Clostridia and Bacteroides. Concentrations of 0.03 to 0.12 microgram per ml inhibit nearly all strains of *S. aureus*. The antibacterial activity of fusidic acid is not diminished in the presence of betamethasone.

5.2 PHARMACOKINETIC PROPERTIES

There are no data which define the pharmacokinetics of Fucibet® Lipid cream, following topical administration in man.

However, *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.

5.3 PRECLINICAL SAFETY DATA

There are no pre-clinical 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

Steareth-21
Cetostearyl alcohol
White soft paraffin
Liquid paraffin
Hypromellose
Citric acid monohydrate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Potassium sorbate
Purified water

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

Unopened container: 2 years

After first opening of container: 3 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium tubes of 5 gram, 15 gram, 30 gram, and 60 grams.

Not all pack sizes are marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

None

7 MARKETING AUTHORISATION HOLDER

LEO Laboratories Limited
Princes Risborough
Bucks
HP27 9RR

8 MARKETING AUTHORISATION NUMBER(S)

PL 00043/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/02/2007

10 DATE OF REVISION OF THE TEXT

06/02/2007

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

Fucibet® Lipid cream

This leaflet gives you some helpful information about Fucibet® Lipid cream. Read the leaflet carefully before you use the cream. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.

What is in Fucibet® Lipid cream?
The active ingredients in Fucibet® Lipid cream are fusidic acid 2% and betamethasone valerate 0.1%.

The cream also contains other ingredients. These are Steareth-21, cetostearyl alcohol, white soft paraffin, liquid paraffin, hypromellose, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate and purified water.

Fucibet® Lipid cream is a white cream available only on prescription in 5 gram, 15 gram, 30 gram and 60 gram aluminium tubes.

Who makes Fucibet® Lipid cream?
The cream is made by LEO Laboratories Limited, 285 Cashel Road, Dublin 12, Ireland.
The Marketing Authorisation Holder is LEO Laboratories Limited, Longwick Road, Princes Risborough, Bucks, HP27 9RR, UK.

How does Fucibet® Lipid cream work?
Fucibet® Lipid cream contains an antibiotic (fusidic acid) and a steroid (betamethasone valerate). (This steroid should not be confused with anabolic steroids misused by some bodybuilders). It works by reducing the swelling, itchiness and redness and by killing the bacteria causing the skin infection.

What is Fucibet® Lipid cream used for?
Your doctor will have prescribed the cream for your particular skin condition. The cream is used to treat inflamed skin conditions such as eczema and dermatitis which are also infected with bacteria. It should not be used for those skin conditions caused only by bacteria e.g. boils and spots, by viruses e.g. cold sores and chicken pox, and by fungi e.g. athlete's foot. It should also not be used to treat acne rosacea or a type of dermatitis with spots around the mouth and chin.

Before you use the cream

As with all prescription medicines:

- tell your doctor if you are pregnant or breast feeding or if you become pregnant during your treatment. Steroids for the skin should not be used in large amounts or for a long time during pregnancy.
- do not use the cream if you are allergic to any of the ingredients as listed above.
- do not use the cream unless your doctor has told you to.

This cream contains cetostearyl alcohol and potassium sorbate which may cause local skin reactions e.g. contact dermatitis. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

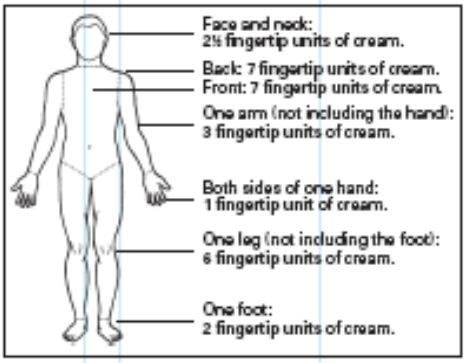
Using the cream

- Follow your doctor's instructions about when and how to use the cream. Your pharmacist will explain if you are not sure. You will find more advice on how much cream to use under the heading ***'How much cream should I use?'***.
- Use the spike in the top of the cap to make a hole through the seal on the tube.
- Put the cream on the affected areas of your skin twice a day but less often if you cover the area with a plaster or any form of bandaging. You will normally do this for 2 weeks.
- Gently rub the cream onto your skin. If you use it on the face, do not get the cream in your eyes. This is because it may cause stinging and rarely loss of vision. If it does get in your eyes, bathe them with a lot of cold water. If you have vision loss, **contact your doctor immediately**.

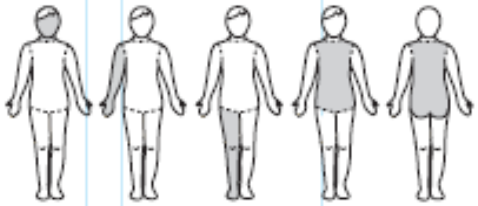
HOW MUCH CREAM SHOULD I USE?

If your doctor has given you specific instructions about the amount then keep to this advice. If not, the following guide will help you to use the correct amount. Use your index finger (first finger) as a measure. Squeeze the cream from the tube along your index finger from the tip to the first joint as shown in the diagram on the left. This amount of cream is one fingertip unit. One fingertip unit is the amount of cream squeezed along your index finger to the first joint.

For adults
The diagram adjacent shows you how much cream you need to cover different areas of your body.
If you find you need slightly more or less cream than indicated, do not worry as this is only a general guide.



For children 6-10 years
Use an adult fingertip unit to measure the amount of cream needed.
From the table adjacent, you can work out the amount of cream you need to cover the areas shown, depending on the age of your child.



Child's age	Number of fingertip units needed				
	Face and neck	Arm and hand	Leg and foot	Front	Back including buttocks
6-10 years	2	2½	4½	3½	5

What should I do if I forget to use the cream?

- If you forget to use your cream at the right time, use it as soon as you remember. Then continue as before.

After you use the cream

- You should notice an improvement after just a few days of using the cream. So, if there is no improvement after 7 days you should stop using your cream and go back to your doctor.
- Most people find using this cream causes no problems, but as with other similar treatments used on the skin:
  - the cream may irritate your skin slightly for a short while after you have put it on. Do not worry, but see your doctor if this carries on, or if you have any other problems.
  - if you use the cream over a long time or in large amounts, it may increase the chance of your skin becoming sensitive (you may notice some burning or stinging when you use the cream and your skin may look redder or itch more than usual).Thinning of the skin and the appearance of small veins may occur, particularly in skin folds or if the affected area is covered with a plaster or bandage. Rarely you may have a skin rash (contact dermatitis).
  - sometimes your skin infection does not get better even though you are using the cream as your doctor has told you. This may be because the cream is no longer killing the bacteria causing the infection. If this happens see your doctor.
  - if you use the cream continuously for a long time over large areas of the body your face may become puffy. Children are at particular risk.
- If you get any cream in your eyes, bathe them with plenty of cold water. If you have vision loss, contact your doctor immediately.
- Remember this treatment is for you. Only a doctor can prescribe it for you. Do not let other people use your treatment even if their skin problem seems to be the same as yours.
- If you notice these or any other side effects and you are concerned tell your doctor or pharmacist.

Storing the cream

- Keep the tube in a safe place where children cannot see or reach it
- Do not store above 25°C.
- Store in original container.
- Do not use the cream after the date on the tube. The tube should be discarded 3 months after first opening. Make a note of the date you first opened the tube in the space provided on the carton.

The Leaflet was written: October 2006

® Registered Trade Mark

LEO

LABELLING

Label for pack size 5g

Fucibet® Lipid cream

5g

Contains:
Fusidic Acid 2% w/w and Betamethasone 0.1% w/w (as the valerate ester).
Other ingredients: Steareth-21, cetostearyl alcohol, white soft paraffin, liquid paraffin, hypromellose, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate and purified water.
See leaflet for further information.

For external use only
For application to the skin
To be used as directed by a physician
Keep out of the reach and sight of children.
Do not store above 25°C. Store in original container. Discard the tube 3 months after first opening.

PL 00043/0218

POM

L E O

LOT:

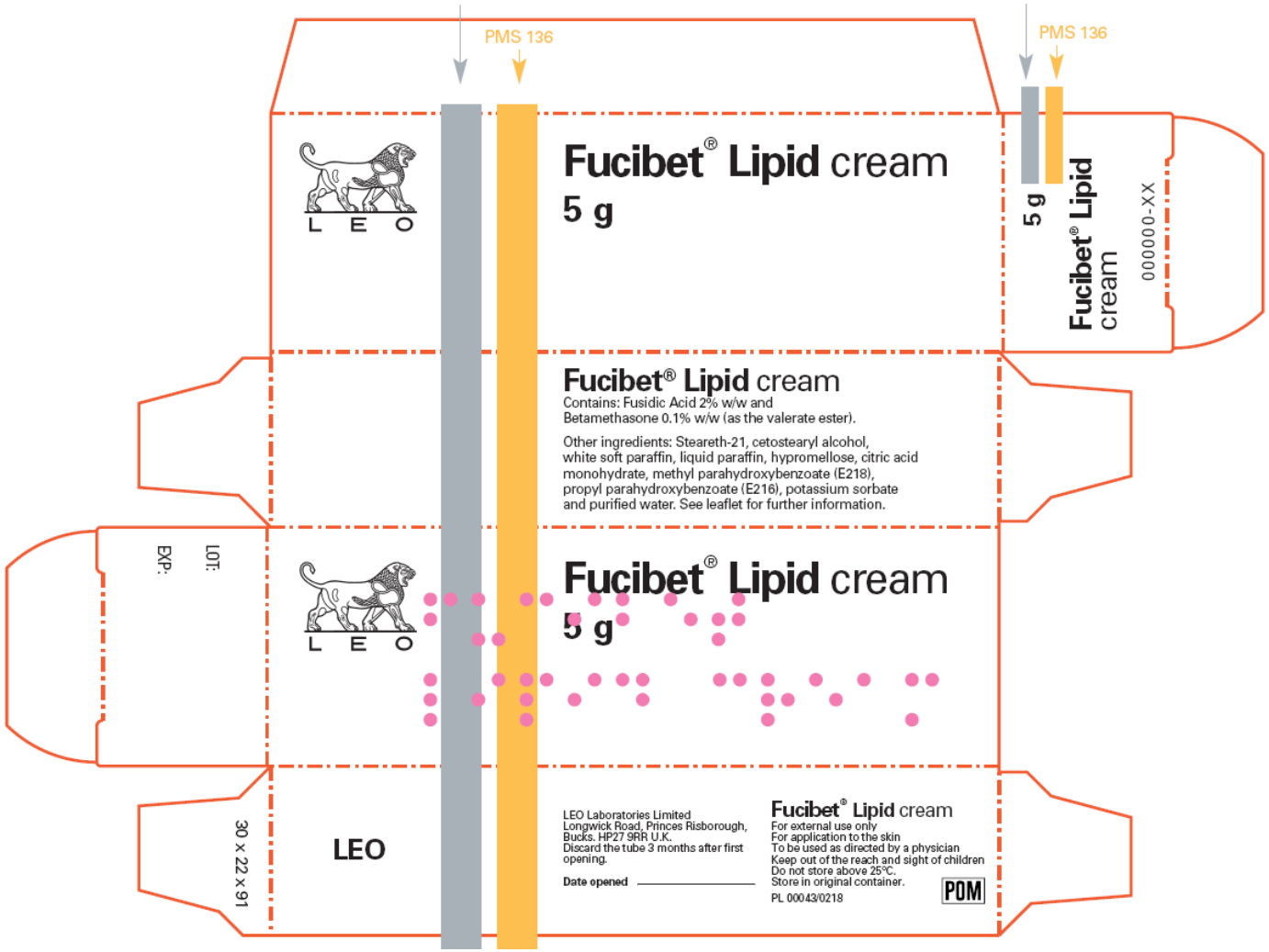
LEO
Laboratories Limited
Longwick Road
Princes Risborough
Bucks. HP27 9RR
U.K.

LEO

EXP:

000000-XX

Carton for pack size 5g, with braille



Label for pack size 15g

Fucibet® Lipid cream

15 g

Contains:
Fusidic Acid 2% w/w and Betamethasone 0.1% w/w (as the valerate ester).
Other ingredients: Steareth-21, cetostearyl alcohol, white soft paraffin, liquid paraffin, hypromellose, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate and purified water.
See leaflet for further information.

For external use only
For application to the skin
To be used as directed by a physician
Keep out of the reach and sight of children.
Do not store above 25°C. Store in original container. Discard the tube 3 months after first opening.

PL 00043/0218

POM

L E O

LOT:

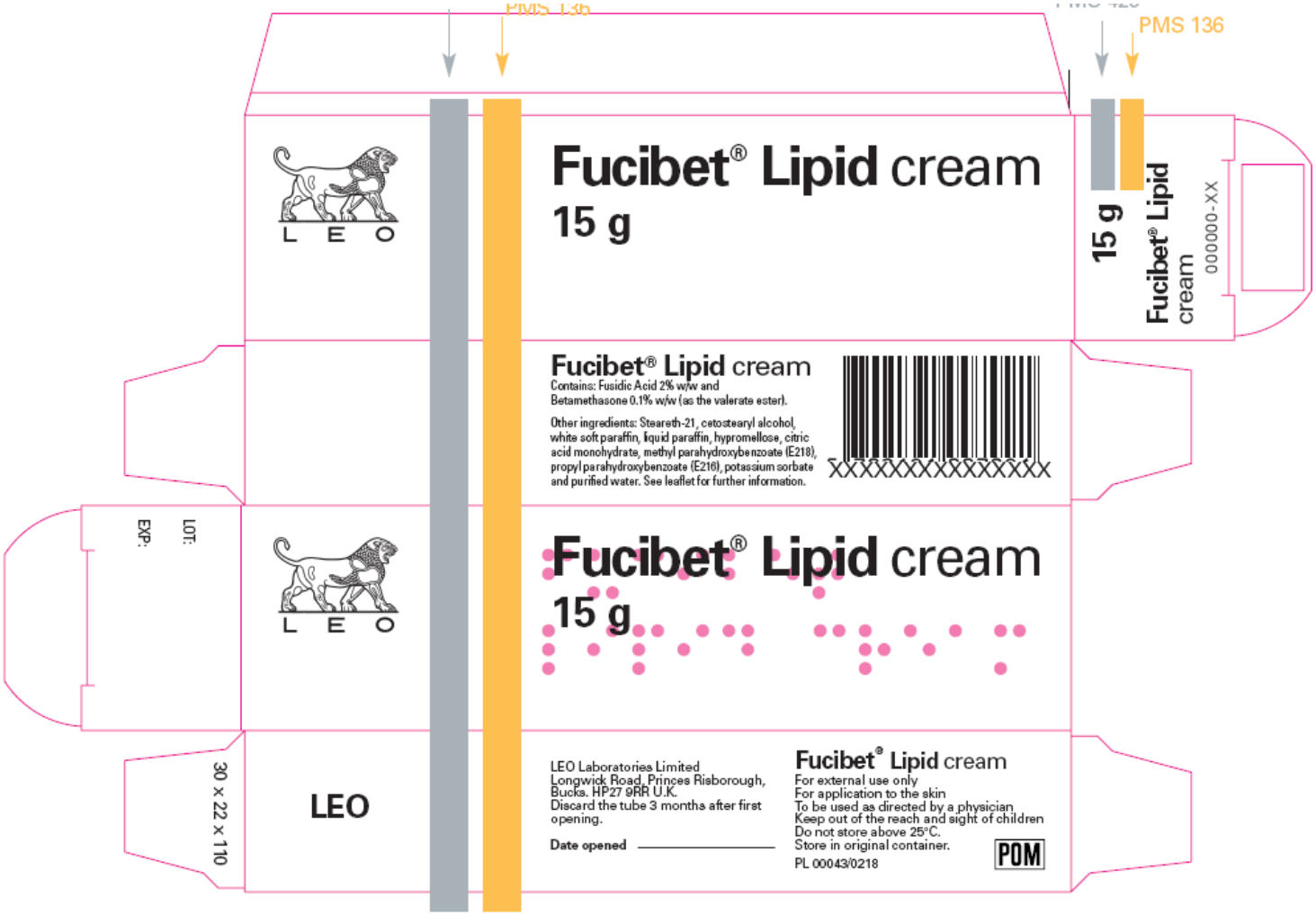
LEO Laboratories Limited
Longwick Road
Princes Risborough
Bucks. HP27 9RR
U.K.

LEO

EXP:

000000-XX

Carton for pack size 15g, with braille



Label for pack size 30g

Fucibet® Lipid cream

30g

Contains:
Fusidic Acid 2% w/w and Betamethasone 0.1% w/w (as the valerate ester).
Other ingredients: Steareth-21, cetostearyl alcohol, white soft paraffin, liquid paraffin, hypromellose, citric acid monohydrate, methyl parahydroxy-benzoate (E218), propyl parahydroxy-benzoate (E216), potassium sorbate and purified water.
See leaflet for further information.

For external use only
For application to the skin
To be used as directed by a physician
Keep out of the reach and sight of children.
Do not store above 25°C. Store in original container. Discard the tube 3 months after first opening.

PL 00043/0218

POM

L E O

LOT:

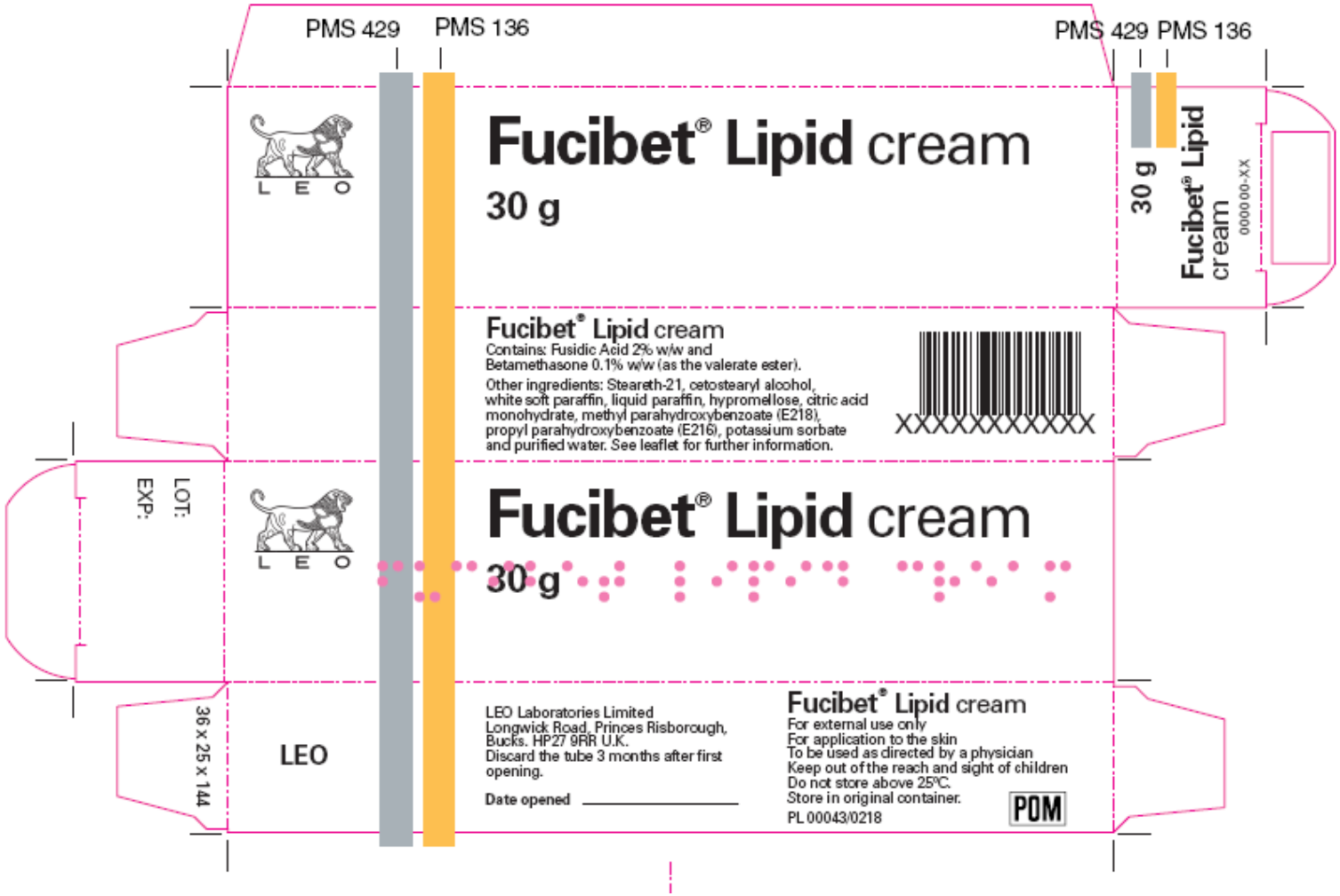
LEO Laboratories Limited
Longwick Road
Princes Risborough
Bucks. HP27 9RR
U.K.

EXP:

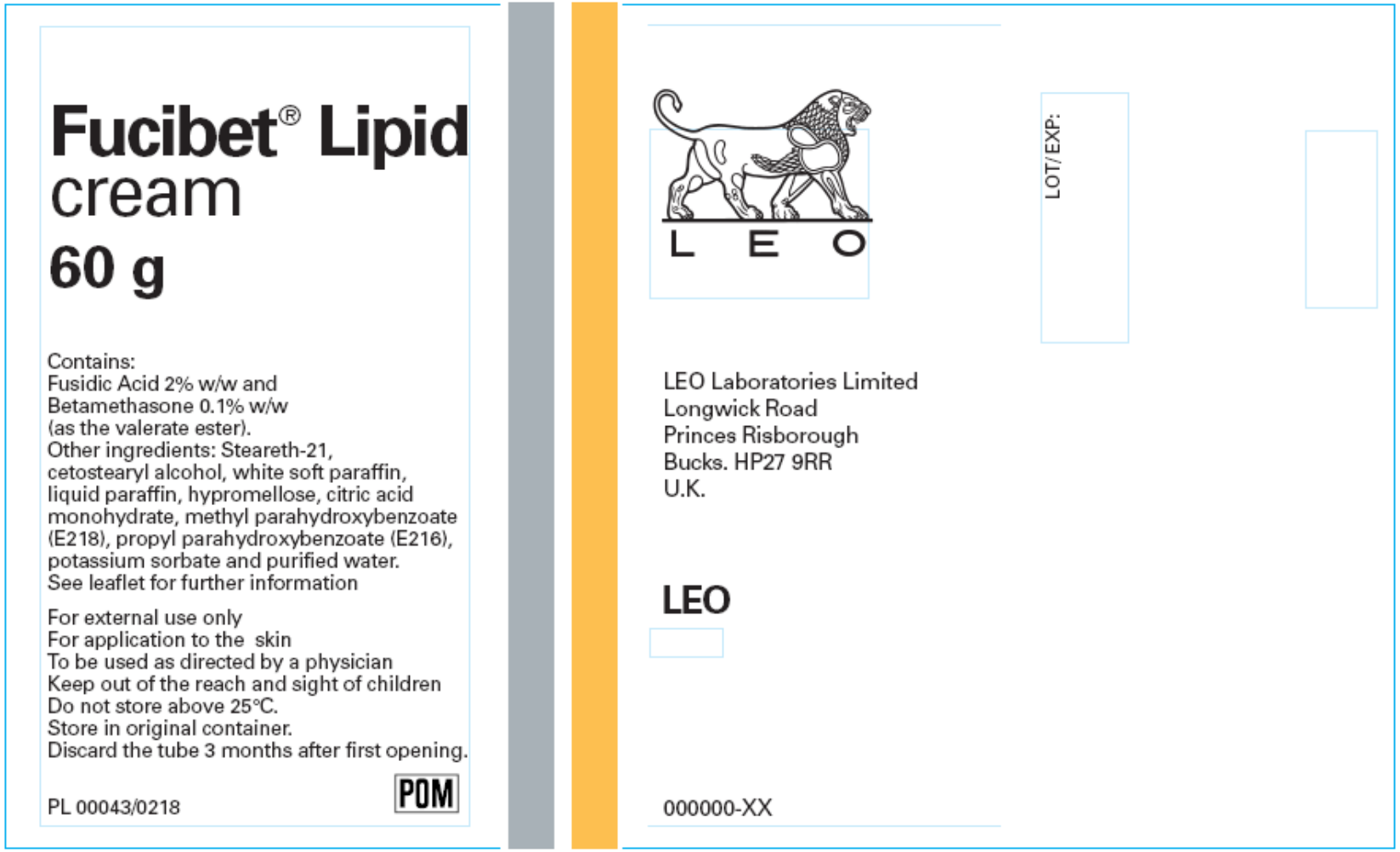
LEO

000000-XX

Carton for pack size 30g, with braille



Label for pack size 60g



Carton for pack size 60g, with braille