PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR FUCIBET®

Fusidic acid and Betamethasone valerate cream

Cream, 2% (w/w) fusidic acid / 0.1% (w/w) betamethasone (as valerate), Topical

Topical Antibiotic / Corticosteroid (D07CC01)

LEO Pharma Inc.
Thornhill, Ontario
L3T 7W8
www.leo-pharma.com/canada

Submission Control No: 203765

Date of Initial Approval:
April 12, 2018

RECENT MAJOR LABEL CHANGES

Not Applicable

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FUCIBET (fusidic acid and betamethasone valerate) is indicated for:

- The topical treatment of eczematous dermatoses including atopic eczema, discoid eczema, stasis eczema and seborrhoeic eczema when secondary bacterial infection caused by *Staphylococcus aureus* is confirmed or suspected.

Due to its betamethasone content, FUCIBET is suitable in cases where treatment with a potent corticosteroid is appropriate to manage the pruritus and inflammation associated with eczematous dermatoses.

FUCIBET is intended for use during flare-ups for short-term (up to 2 weeks) treatment against bacteria susceptible to fusidic acid (see MICROBIOLOGY).

FUCIBET contains an antibacterial ingredient, fusidic acid. To reduce the development of drug-resistant bacteria and maintain the effectiveness of fusidic acid, FUCIBET should only be used to treat infections that are proven or strongly suspected to be caused by bacteria.

1.1 Pediatrics (6 to <18 years of age):

The safety and efficacy of FUCIBET in pediatric patients six years of age and older has been established. However, FUCIBET should be used with care in children as pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than adult patients (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

1.2 Geriatrics (≥ 65 years of age):

The observed safety and efficacy profile for FUCIBET in older patients is similar to that in younger adults.

2 CONTRAINDICATIONS

FUCIBET is contraindicated in:

- Patients who are hypersensitive to fusidic acid/sodium fusidate, betamethasone valerate or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with the following conditions (due to the potential for systemic or local effects related to the betamethasone component):
    - Systemic fungal infections
    - Primary skin infections caused by fungi, virus or bacteria
    - Skin eruptions associated with tuberculosis or syphilis
    - Perioral dermatitis and rosacea
    - Eruptions following vaccinations

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- For topical use only
- For use in adults and children aged 6 years and older

3.2 Recommended Dose and Dosage Adjustment

Adults and children: Use twice daily until a satisfactory response is obtained. A single treatment course should not exceed 2 weeks.

Pediatrics (6 to <18 years of age): No dosage adjustment is necessary. Avoid use of large amounts of FUCIBET, occlusion or prolonged treatment, since pediatric patients may demonstrate greater susceptibility to corticosteroid-induced reactions (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Geriatrics (> 65 years of age): No specific precautions and no dosage modifications are necessary in elderly patients.

Renal impairment: No dosage modifications should be necessary in patients with renal impairment.

Hepatic impairment: No dosage modifications should be necessary in patients with hepatic impairment.

3.3 Administration

A thin layer should be applied to cover the affected skin area. Due to the content of corticosteroid, avoid getting FUCIBET in the eyes (WARNINGS AND PRECAUTIONS Ophthalmologic).

3.4 Missed Dose

If a dose is missed, the patient should apply FUCIBET when he/she remembers and then continue as usual for the next application.

4 OVERDOSAGE

For topically applied fusidic acid, no information concerning potential symptoms and signs due to overdose administration is available. Cushing's syndrome and adrenocortical insufficiency may develop following topical application of corticosteroids in large amounts and for more than 3 weeks.

Systemic consequences of an overdose of the active substances after accidental oral intake are unlikely to occur. The amount of fusidic acid in one tube of FUCIBET does not exceed the oral daily dose of systemic treatment. A single oral overdosage of corticosteroids is rarely a clinical problem.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Cream, 2% (w/w) Fusidic acid and 0.1% (w/w) betamethasone (as valerate)	all- *rac*-*α*-tocopherol, cetostearyl alcohol, citric acid monohydrate, hypromellose, liquid paraffin, methyl parahydroxybenzoate, potassium sorbate, propyl parahydroxybenzoate, purified water, steareth-21 and white soft paraffin.

FUCIBET is a white highly viscous oil-in-water emulsion cream containing fusidic acid 2% and betamethasone 0.1% (as the valerate ester).

Available in 15 g and 30 g aluminium tubes.

6 WARNINGS AND PRECAUTIONS

General
Long-term continuous topical therapy with FUCIBET should be avoided. A treatment course should last no longer than two weeks.

Possible systemic absorption of betamethasone valerate should always be considered during treatment with FUCIBET.

When topical corticosteroids (such as betamethasone) are used under occlusive dressing, over extensive areas, or on the face, scalp, axillae and scrotum, sufficient absorption may occur giving rise to adrenal suppression and other systemic effects. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, reduce the frequency of application or to substitute a less potent steroid.

Endocrine and Metabolism
Systemic absorption of topical corticosteroids has caused reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glycosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids.

Fertility
There are no clinical studies with topical FUCIBET regarding fertility.

Hepatic
There are no adequate and well controlled studies of FUCIBET use in patients with hepatic impairment.

Immune
Due to the corticosteroid component having an immunosuppressant effect, FUCIBET may be associated with increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. It is advised to switch to systemic treatment if infected eczema

cannot be controlled with topical treatment.

FUCIBET contains methyl and propyl parahydroxybenzoate (E218 and E216) as excipients. These excipients may cause allergic reactions (possibly delayed).

FUCIBET contains cetostearyl alcohol and potassium sorbate as excipients. These excipients may cause local skin reactions (e.g. contact dermatitis).

Ophthalmologic
Due to the betamethasone component in FUCIBET, use with care near the eyes and avoid getting FUCIBET into the eyes. Raised intra-ocular pressure, glaucoma and cataract may occur after topical use of corticosteroids near the eyes, particularly with prolonged use and in patients predisposed to developing glaucoma and cataract.

Renal
There are no adequate and well controlled studies of FUCIBET use in patients with renal impairment.

Susceptibility/Resistance
Development of Drug Resistant Bacteria
Using FUCIBET in the absence of a proven or strongly suspected bacterial infection may risk the development of drug-resistant bacteria.

Potential for Microbial Overgrowth
Bacterial resistance has been reported to occur with the topical use of fusidic acid. As with all antibiotics, extended or recurrent application may increase the risk of developing antibiotic resistance. Limiting therapy with topical fusidic acid and betamethasone valerate to treatment courses of no more than 2 weeks at a time will minimise both the risk of developing resistance and the risk of overgrowth of non-susceptible microorganisms, including fungi.

This also lessens the risk that the immunosuppressive action of corticosteroid might mask any potential symptoms of infections due to antibiotic-resistant bacteria.

Skin
Due to the content of betamethasone valerate, prolonged topical use of FUCIBET may cause skin atrophy. Other undesirable dermatological class effects of potent corticosteroids (for e.g. betamethasone) include: dermatitis (such as dermatitis contact, dermatitis acneiform and perioral dermatitis), skin striae, telangiectasia, rosacea, erythema, hypertrichosis, hyperhydrosis and depigmentation. Ecchymosis may also occur with prolonged use of topical corticosteroids.

6.1 Special Populations

6.1.1 Pregnant Women

The safety of fusidic acid and/or topical betamethasone valerate during pregnancy has not been established. The use of FUCIBET during pregnancy requires that the potential benefits be weighed against the risks to the foetus. Due to the presence of betamethasone, FUCIBET should not be used on pregnant patients in large amounts, or for prolonged periods of time.

Fusidic acid: No effects during pregnancy are anticipated, since systemic exposure to fusidic acid is negligible. Studies in animals have not shown teratogenic effects with fusidic acid. Limited studies in animals have shown negligible systemic absorption of topical fusidic acid.

Betamethasone valerate: There is a limited amount of data from the use of topical betamethasone valerate in pregnant women. Studies in animals have shown reproductive toxicity/foetal abnormalities (see TOXICOLOGY). Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development, including cleft palate and intr-uterine growth retardation. There may, therefore be a risk of such effects to the fetus.

6.1.2 Breast-feeding

The safety of fusidic acid and/or betamethasone valerate during lactation has not been established. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Following systemic administration, fusidic acid and corticosteroids have been detected in the milk of nursing mothers. Administration of FUCIBET during lactation should only be considered if the expected benefit to the mother outweighs the risk to the nursing infant.

It is recommended to avoid applying FUCIBET on the breast to protect the nursing infant from unintentional oral drug uptake.

6.1.3 Pediatrics (6 to <18 years of age)

FUCIBET should be used with care in children as pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than adult patients. This is due to increased systemic absorption of betamethasone as a result of a larger skin surface area to body weight ratio in children. Children may also be at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Large amounts, occlusion or prolonged treatment with FUCIBET should be avoided (see ADVERSE DRUG REACTIONS).

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

Recognised side effects with topical corticosteroid-antibiotic combinations can be differentiated according to the individual components of the combination. In the case of topical corticosteroids the most common side effects reported are skin atrophy, application site irritation, skin discolouration, and striae. The side effect most frequently reported with topical antibiotic treatments is contact dermatitis, and the incidence is dependent on the antibiotic agent used. In the case of fusidic acid the reported rates of contact dermatitis range between 0.3% and ≤0.8%.

The most frequently reported adverse reaction during treatment with FUCIBET is pruritus.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study FCF0001 was a randomised, double blind, three arm, parallel group, active and vehicle controlled comparative phase III study in patients with atopic dermatitis. A total of 629 patients were randomized to twice daily treatment for 2 weeks with either FUCIBET (lipid cream, 275), fusidic acid/betamethasone valerate cream (264), or the lipid cream vehicle (90).

In the FUCIBET group rates of adverse events were 13.5% compared with 21.6% in the vehicle group. Lesional/peri-lesional adverse events seen with FUCIBET were 2.6% versus 13.6% for the vehicle. The most frequently reported adverse drug reactions were pruritus and skin burning sensation.

7.3 Less Common Clinical Trial Adverse Reactions (<1%)

General disorders and administration site conditions: Application site pain, application site irritation, application site swelling, and application site vesicles.

Skin and subcutaneous tissue disorders: Eczema (condition aggravated), skin burning sensation, pruritus, dry skin, erythema, urticaria, rash (including rash erythematous and rash generalised)

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The effect of FUCIBET on laboratory tests has not been established.

7.5 Post-Market Adverse Reactions

The following post-market adverse drug reactions have been reported with FUCIBET.

Immune system disorders: Hypersensitivity

Skin and subcutaneous tissue disorders: Dermatitis contact

8 DRUG INTERACTIONS

8.1 Overview

No interaction studies have been performed.

8.2 Drug-Drug Interactions

At recommended doses, FUCIBET is not known to cause medically significant drug interactions.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

FUCIBET is a combination preparation containing the corticosteroid, betamethasone valerate, and the antibiotic, fusidic acid.

Betamethasone belongs to the group of potent corticosteroid (class III) and has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory

activity of topical corticosteroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostagladins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Fusidic acid inhibits bacterial protein synthesis. The drug interferes with amino acid transfer from aminoacyl-tRNA to protein on the ribosomes. Fusidic acid is primarily active against Gram-positive bacteria, in particular *S.aureus* including methicillin-resistant *S. aureus* (MRSA). Fusidic acid is also active against *Streptococcus spp., Corynebacterium minutissimum, some Neisseria spp.,* and certain *Clostridium spp*. The action of fusidic acid is mainly bacteriostatic but, at higher concentrations, may be bactericidal.

9.2 Pharmacokinetics

There are no data which accurately define the pharmacokinetics of FUCIBET following topical administration in man.

Absorption
As with many topically delivered drugs, dermal absorption of fusidic acid and betamethasone is difficult to quantify, but is generally accepted to be low in relation to systemic administration. The degree of penetration depends on factors such as the duration of exposure and the condition of the skin and the site of application.

In vitro studies showed that up to 2.5% of topically applied fusidic acid could cross intact human skin within 30 minutes and that up to 10% of the applied dose could penetrate down into the stratum corneum of the skin, reaching levels well above the minimum inhibitory concentration (MIC) required for sensitive *S. aureus* strains.

In vivo and *in vitro* studies suggest that there is only negligible systemic absorption of topically administered fusidic acid.

Betamethasone valerate is absorbed following topical administration. Occlusion of the treated area under plastic material greatly increases the absorption.

Distribution: Corticosteroids are bound to plasma proteins in varying degrees and widely distributed in the peripheral tissue and organs.

Metabolism: Once absorbed through the skin, topical corticosteroids undergo the same pharmacokinetic pathways as systemically administered corticosteroids. Corticosteroids are metabolized primarily in the liver by CYP3A4. Fusidic acid is metabolized primarily in the liver. The half-life of fusidic acid is variable from 5 to around 16 hours.

Excretion: Corticosteroids and their metabolites are conjugated in the liver and kidneys with sulphate or glucuronic acid and excreted in urine. In addition, some corticosteroids and their metabolites are also excreted in the bile. Fusidic acid is excreted mainly in the bile with little excreted in the urine.

Special Populations and Conditions

Pediatrics (6 to <18 years of age): Adrenal suppression can occur with long-term continuous topical therapy with FUCIBET or use of large amounts even without occlusion.

10 STORAGE, STABILITY AND DISPOSAL

Store at or below 25˚C. Use within 3 months after first opening of container.

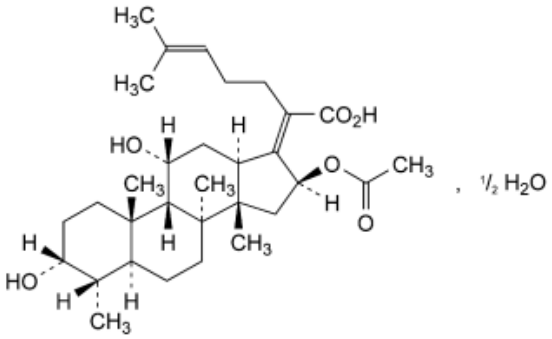
PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

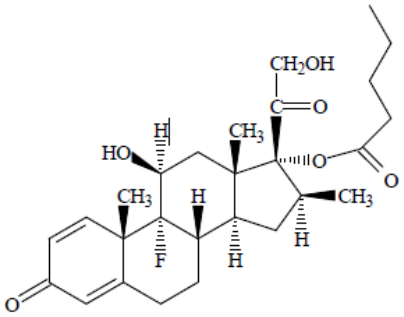
Drug Substance

Proper name (I.N.N.):	Fusidic acid	Betamethasone 17-valerate
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	9-fluoro-11 β, 17, 21-trihydroxy-16 β -methylpregna-1, 4-diene-3,20-dione 17-valerate
Molecular formula:	$C_{31}H_{48}O_6$	$C_{27}H_{37}FO_6$
Molecular mass:	516.7 g/mol (as anhydrate) 525.7 g/mol (as hemihydrate)	476.58 g/mol
Chirality:	Geometrical isomerism around C-17 and C-20	8 stereogenic centers, in 8, 9, 10, 11, 13,14, 16 and 17 position
Physicochemical properties :	Fusidic acid	Betamethasone valerate
Physical form:	White or almost white microcrystalline powder	White or almost white microcrystalline powder
Solubility:	Freely soluble in alcohol, insoluble in water, and insoluble in the oil-in-water formulation of the drug product.	Soluble in alcohol, insoluble in water, and insoluble in the oil-in-water formulation of the drug product.
Melting point:	177-179°C	185-195°C
Polymorphism:	Only one hemihydrate can be obtained	No evidence of polymorphic transformation
Other characteristics:	Sensitive to light and prone to oxidation	Sensitive to light and prone to oxidation

Structural formula:
Fusidic acid hemihydrate



Betamethasone valerate



12 CLINICAL TRIALS

Study FCF0001 was a randomised double blind, three arm, parallel group, active and vehicle controlled comparative phase III study in patients with clinically infected atopic dermatitis. A total of 629 patients were randomized to twice daily double-blind treatment for 2 weeks with either FUCIBET (lipid cream), fusidic acid/betamethasone valerate cream, or the lipid cream vehicle.

12.1 Trial Design and Study Demographics

Table 1 - Summary of patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)
FCF0001 INT	Prospective, randomised, double-blind, 3-arm parallel group, active and vehicle-controlled	2 weeks; twice-daily	N = 629; fusidic acid/ betamethasone valerate cream (264); Fucibet® (lipid cream) (275); Lipid cream vehicle (90)	Mean age (range), 25.6 (3-78) years

The primary endpoint for overall clinical response was the percentage reduction/change in total severity scores (TSS) from baseline to end of treatment. TSS was calculated based on the severity of erythema, edema, oozing/crusting and excoriation, each assessed at a 4-point scale. In addition, for overall treatment efficacy patients with marked improvement or complete clearance were defined as responders.

12.2 Study Results

Study results are provided for FUCIBET versus lipid cream vehicle. The mean percentage reductions in TSS of the target lesion from baseline to end of treatment were approximately 82.9% in the FUCIBET group and 33% in the lipid cream vehicle group. The estimated treatment difference between the FUCIBET group and the lipid cream vehicle group was statistically significantly different ($p<0.001$) demonstrating a statistically significantly superior effect of the lipid cream as compared with the vehicle.

At end of treatment, approximately 83% of the patients in the FUCIBET group and approximately 30% of patients in the vehicle group were responders. The difference between the proportion of responders in the lipid cream group and the vehicle group was statistically significant ($p<0.001$) in favour of FUCIBET.

Successful bacteriological response obtained for the FUCIBET group (88%) was statistically significantly superior to that for the lipid cream vehicle group (25%).

13 MICROBIOLOGY

The microbiological effect of FUCIBET (fusidic acid and betamethasone valerate) is attributed to fusidic acid. Fusidic acid is a narrow-spectrum antibiotic, predominantly active against Gram-positive bacteria and specifically, *Staphylococci* including MRSA (see Table 2 below) and *Corynebacteria*. Notably, it is highly effective against *S. aureus*, including methicillin-resistant strains, at MIC90 concentrations of 0.25 mg/l.

Table 2. Anti-staphylococcal Activity of Fusidic Acid

		Minimum Inhibitory Concentration, (mg/L)		
Organism	**No. of isolates**	**MIC_{50}**	**MIC_{90}**	**MIC Range**
S. aureus	879	0.125	0.25	0.03 - 2
Methicillin-susceptible *S. aureus* (MSSA)	26	0.125	0.25	≤0.06 - 2
Methicillin-resistant *S. aureus* (MRSA)	126	0.125	0.25	≤0.06 - 0.5
Coagulase negative *staphylococci* (methicillin susceptible)	26	0.125	2	0.125 - 16
Coagulase negative *staphylococci* (methicillin resistant)	125	0.125	0.25	≤0.06 - 8

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) website contains MIC distribution data for fusidic acid. The epidemiological breakpoint (ECOFF) for fusidic acid is set by EUCAST to 0.5 mg/L for *S. aureus*, irrespective of their susceptibility to methicillin. The same breakpoint is used for the most prevalent coagulase negative *Staphylococci* (*S. epidermidis*, *S. lugdunensis* and *S. haemolyticus*).

13.1 Susceptibility

Fusidic acid is primarily active against Gram-positive bacteria, in particular *S.aureus* including MRSA.

Fusidic acid is also active against against a number of other Gram-positive bacteria and a few Gram-negative bacteria (see Table 3 below) – certain *Streptococcus spp., Corynebacterium minutissimum,* some *Neisseria spp.*, and certain *Clostridium spp.* Most Gram-negative bacteria (including *Haemophilus influenza*, *Enterobactericeae* such as *Escherichia coli* and *Klebsiella pneumonia* and *Pseudomonas* spp.) are resistant to fusidic acid/sodium fusidate.

Table 3. Activity of Fusidic Acid against Bacterial Species other than Staphylococci

		Minimum Inhibitory Concentration, (mg/L)		
Organism	**No. of isolates**	**MIC_{50}**	**MIC_{90}**	**MIC Range**
Streptococci - Group A	102	4	8	1-32
Clostridium difficile	80	0.75	2	0.125-4
Propionibacterium acnes	50	-	1	-
Bacteroides fragilis	23	-	8	-
Corynebacterium minitissimum	20	0.03	0.06	≤0.015-0.25
Neisseria meningitis	100	0.03	0.12	≤0.015-0.5

13.2 Development of Resistance

Fusidic acid is the sole fusidane and is chemically distinct to other antibiotics. Due to its unique molecular structure and distinct mode of action, target specific cross-resistance with other classes of antibacterial agents has not been detected.

In a sensitivity study of 2,302 *S. aureus* strains isolated from clinical specimens over a 6 year period, 65 strains (2.8%) were found to be resistant to fusidic acid, and bi-annual resistance rates ranged from 0.7 to 6.3%. Among the 2,302 strains tested there were 240 MRSA strains detected, of which 10 (4.2%) were also resistant to fusidic acid.

To date, five genes (*fusA*, *fusB*, *fusC*, *fusD* and *fusE*) have been associated with fusidic acid resistance. Resistant strains isolated from the clinical setting may exhibit reduced growth rate and lower pathogenicity and can revert to full susceptibility in the absence of fusidic acid. Management and prevention of the spread of fusidic acid resistance in *S. aureus* has benefited from characterization of the five resistance genes. In *S. aureus* two main types of resistance mechanisms have been characterized. The first is caused by mutations in the fusidic acid

binding site of EF-G (*fusA*) and the other involves horizontal acquisition of determinants encoding *FusB* -type resistance determinants (*fusB* and *fusC*) that binds to EF-G.

14 NON-CLINICAL TOXICOLOGY

Most of the toxicology studies conducted in animals were performed using systemic administration, hence achieving markedly higher concentrations than obtained with topical administration. Fusidic acid and betamethasone showed only limited toxicity in these studies with adult animals. No studies have been conducted with juvenile animals.

14.1 Single Dose Toxicity

Fusidic acid: No acute dermal toxicity studies have been performed with fusidic acid.
Mice and rats (5 males + 5 females per group) were given a single dose of fusidic acid (suspended in 0.25% w/v methocel) by the oral (p.o.) or intraperitoneal (i.p.) route. The oral administration of fusidic acid induced clinical signs of decreased locomotor activity up to 4 hours after the treatment in the mice, but no signs were observed in the rats. The i.p. administration of fusidic acid caused decreased locomotor activity from 2-3 hours until 2-3 days after the treatment in the mice and up to 24 hours in the rats. The median lethal dose (LD_{50}) was determined (see Table 4). At the autopsy, no abnormalities were found in the animals treated orally. In the animals treated i.p., peritoneal haemorrhage, ascites and residues of test substance in the abdominal cavity were found.

Table 4. Fusidic acid LD_{50}-values

Route	LD_{50} mouse (mg/kg)	LD_{50} rat (mg/kg)
Oral	>5000	>5000
Intraperitoneal	3900	3550

Betamethasone: No data are available on betamethasone valerate. Betamethasone dipropionate showed a low acute toxicity in rats with LD_{50} values above 4000 mg/kg for both genders when given orally.

14.2 Repeat Dose Toxicity

Fusidic acid: No repeat dose dermal toxicity studies have been performed with fusidic acid.
In a 5-months oral toxicity study in rats, fusidic acid was suspended in a saccharose solution and administered orally by gavage to one group of 25 male + 25 female rats of the local LEO strain. Daily doses of 400 mg/kg fusidic acid were administered 6 days a week for 5 months. A control group of 10 male + 10 female rats was treated with the sugar solution. The clinical appearance, body weight and haematology parameters were recorded.

No haematological changes and no gross pathological changes were apparent throughout the test period. Microscopic examination of lung, heart, spleen, liver kidney, stomach and intestine did not disclose any morphological alterations that could be attributed to the drug.

Betamethasone: No data are available in the literature with respect to repeat-dose toxicity of betamethasone valerate in animals.

Repeat-dose studies in mice (13 week dermal) and rats (13 week oral, 26 week subcutaneous) have been performed with the related corticosteroid betamethasone dipropionate. After repeated administration, the pathological findings primarily consisted of atrophy of lymphoid organs (spleen and thymus) and adrenals along with haematological changes (leucopenia/lymphopenia). These effects were observed in the rat at oral and subcutaneous doses from10 µg/kg and in the mouse at dermal doses from 33 µg/kg. These observations are consistent with the known pharmacological properties of betamethasone dipropionate.

14.3 Genotoxicity

Fusidic acid: Fusidic acid was negative in the Ames mutagenicity assay and in an in vivo Micronucleus Test. Fucidic acid is not considered to be genotoxic.

Betamethasone: No data are available on betamethasone valerate. The related substance, betamethasone dipropionate, did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or the rat micronucleus test.

14.4 Carcinogenicity

Fusidic acid: No carcinogenicity testing has been performed with fusidic acid. The genotoxicity tests did not indicate any mutagenic or clastogenic potential and no hormonal effects have been demonstrated.

Betamethasone: No data are available on betamethasone valerate.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages of 1.3, 4.2 and 8.5 µg/kg/day in females, and 1.3, 4.2 and 12.9 µg/kg/day in males (corresponding to dosages of up to approximately 26 µg/m^2/day and 39 µg/m^2/day, in females and males, respectively), no significant changes in tumour incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60 and 200 µg/kg/day (corresponding to dosages of approximately 120, 360 and 1200 µg/m^2/day), no significant changes in tumour incidence were observed when compared to control.

14.5 Reproductive and Developmental Toxicity

Fusidic acid: Preclinical studies and clinical experience indicate that fusidic acid does not have an effect on fertility. Furthermore, *in vivo* and *in vitro* studies indicate negligible systemic absorption of topically administered fusidic acid resulting in negligible risk of adverse effects during pregnancy.

Betamethasone: No data are available on betamethasone valerate.

Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at dosages of 156 µg/kg/day (468 µg/m^2/day) and 2.5 µg/kg/day (30 µg/m^2/day), respectively. Those dose levels are lower than the maximum topical dose of fusidic acid/betamethasone valerate cream in humans (about 5,950 µg/m^2/day).The abnormalities observed included umbilical hernia, exencephaly and cleft palate.

Betamethasone dipropionate was evaluated when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 100, 300, and 1000 µg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

Studies in male rats at oral doses of up to 200 µg/kg/day (1200 µg/m^2/day), and in female rats at oral doses of up to 1000 µg/kg/day (6000 µg/m^2/day) of betamethasone dipropionate indicated no impairment of fertility.

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations, and low birth weight).

14.6 Local Tolerance

In two studies fusidic acid/betamethasone valerate cream was administered daily for up to 6 weeks on shaved New Zealand White rabbits. Mild reactions were seen in a low numbers of animals. Transient severe reactions were seen in three out of five high-dose animals during Week 2 of treatment and in one intermediate-dose animal (out of five) during the last 8 days of treatment.

In vitro studies have demonstrated no significant difference between FUCIBET and fusidic acid/betamethasone valerate cream in permeation through barrier-impaired skin, indicating that the systemic exposure of each of the active ingredients in FUCIBET is no more than that of fusidic acid/betamethasone valerate cream. FUCIBET irritancy relative to a placebo control (lipid cream base) was assessed in a 3-week study in rabbits. Findings consisted of very mild erythema. Both FUCIBET and the vehicle cream appeared well tolerated by rabbits.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PRFUCIBET®
Fusidic acid and Betamethasone valerate

Read this carefully before you start taking Fucibet® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Fucibet®.

What is Fucibet® used for?
Eczema or dermatitis is an irritated skin condition that comes and goes. The skin is red, itchy inflamed and may have oozing blisters or crusting. Eczema lesions can get infected when the skin cracks or splits. Fucibet® is used to treat eczema that is infected with bacteria or appears to be infected.

Fucibet® contains an antibiotic called fusidic acid. Use Fucibet® exactly as your healthcare professional tells you. Using Fucibet® incorrectly or using too much could lead to the growth of bacteria that cannot be killed by this medicine. If this happens, Fucibet® or other medicines with fusidic acid may not work for you in the future. Do not share this medicine.

How does Fucibet® work?
Fucibet® contains two medicines that work together in different ways:
- Fusidic acid is an antibiotic that kills bacteria.
- Betamethasone is a steroid that reduces swelling, redness, pain and itchiness in the skin.

What are the ingredients in Fucibet®?
Medicinal ingredients: fusidic acid and betamethasone valerate
Non-medicinal ingredients: all- *rac*-*α*-tocopherol, cetostearyl alcohol, citric acid monohydrate, hypromellose, liquid paraffin, methyl parahydroxybenzoate, potassium sorbate, propyl parahydroxybenzoate, purified water, steareth-21 and white soft paraffin.

Fucibet® comes in the following dosage forms:
Fucibet® is a white cream containing 2% fusidic acid and 0.1% betamethasone (as valerate). The high lipid content in this cream helps relieve the dry feeling of the skin.

Do not use Fucibet® if:
- You are allergic to any of the ingredients in Fucibet® (see above) or the materials of the container.

Do not use to treat an area of skin where:
- You have a fungal infection (such as athlete's foot or ringworm)
- You have a skin infection not related to your eczema caused by a virus or bacteria
- You have a skin condition related to tuberculosis or syphilis
- You have perioral dermatitis (rash around the mouth) and rosacea (red flushed facial skin).
- You have a rash on the skin where you received a vaccination

To help avoid side effects and ensure proper use, talk to your healthcare professional

before you use Fucibet®. Talk about any health conditions or problems you may have, including if:

- Your infection or eczema gets worse, you get new infected lesions, or you have any other skin reactions
- You use other medicines that contain steroids
- You are pregnant or planning to get pregnant
- You are breast-feeding or plan to breast-feed

Other warnings you should know about:

- Use with care around the eye area. Avoid getting Fucibet® in your eyes
- Using Fucibet® near the eye area may cause glaucoma (increased pressure in your eye) or cataracts (clouding of the lens of your eye). See table of "Serious side effects and what to do about them" below
- Using Fucibet® for more than 2 weeks or in large amounts, may increase your chance of experiencing side effects.
- Do not wrap or bandage the area treated by Fucibet®
- Fucibet® contains methyl and propyl parahydroxybenzoate, cetyl alcohol and potassium sorbate. These ingredients may cause a red, itchy rash (contact dermatitis) on your skin where Fucibet® is applied or cause allergic reactions. Talk to your doctor if you experience any of these side effects while using Fucibet®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Fucibet®:
There are no drugs known to interact with Fucibet®.

How to apply Fucibet®:
Apply a thin layer of cream to cover the affected skin area. Wash your hands after applying to avoid accidentally spreading Fucibet® to healthy skin areas.

Usual dose:
Use Fucibet® twice daily. Do not use for longer than 2 weeks.

Overdose:
Using this drug for longer than recommended can lead to medical conditions, such as Cushing's syndrome or adrenal suppression.

Accidentally swallowing Fucibet® is not likely to lead to any serious side effects.

If you think you have taken too much Fucibet® contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply Fucibet®, apply it as soon as you remember. Then continue as usual for your next application.

What are possible side effects from using Fucibet®?
Common side effects are itching, skin rash (contact dermatitis), stretch marks (striae), skin

discoloration and thinning of the skin (atrophy).

Less common side effects include a burning sensation of the skin, dry skin, redness of the skin, small fluid filled blisters and pain, irritation or swelling of the treated skin area. Most side effects are mild to moderate.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic Reactions: Dizziness, itching, severe rash, swelling (mouth, throat, lips, hands)), trouble breathing.			**X**
Worsening of eczema: Increased itching, redness, swelling		**X**	
Adrenal effects: Fatigue, increased urination / thirst, problems controlling blood sugar levels, weakness, weight loss.		**X**	
Glaucoma: Hazy or blurred vision severe eye and head pain, nausea or vomiting (accompanying severe eye pain), sudden sight loss		**X**	
Cataracts: Clouded, blurred or dim vision.		**X**	

These are not all the possible side effects that you may have when using Fucibet®. If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at or below 25°C. Use within 3 months of first opening the tube and before the expiry date. Keep out of reach and sight of children.

If you want more information about Fucibet®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.leo-pharma.ca, or by calling 1-800-668-7234.

This leaflet was prepared by LEO Pharma Inc.

Last Revised April 12, 2018