Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Fucidin LEO tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of sodium fusidate.

Excipient with known effect:

Each tablet contains lactose monohydrate 71.9 mg.

Each tablet contains sodium 11 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white greyish marbled film-coated oval biconvex tablet without embossing.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of infections caused by Staphylococcus.

4.2 Posology and method of administration

Posology

Adults only:

The usual total daily dose is 1500 mg in divided doses.

In severe infections doses may be doubled or appropriate combined therapy may be used.

Since fusidic acid is excreted in the bile, no dosage modifications are needed in renal impairment.

The dosage in patients undergoing haemodialysis needs no adjustment as fusidic acid is not significantly dialysed.

Paediatric population

Children:

The usual total daily dose is 20 to 50 mg/kg in divided doses.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Statins (HMG-CoA reductase inhibitors) and systemic Fucidin Leo must not be co-administered. There have been reports of rhabdomyolysis (including fatalities) in patients receiving this combination (see section 4.5). In patients where the use of systemic Fucidin is considered essential, statin treatment should be discontinued throughout the duration of treatment with systemic Fucidin Leo. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of systemic Fucidin Leo. In exceptional circumstances, where prolonged systemic Fucidin is needed e.g. for the treatment of severe infections, the need for co-administration of HMG-CoA reductase inhibitors and systemic Fucidin should only be considered on a case by case basis and under close medical supervision.

In a few cases, serious cutaneous reactions putting life at risk such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with systemic Fucidin. Patients should be advised to monitor cutaneous reactions as well as signs and symptoms suggestive of these reactions which usually appear in the first weeks of therapy. If such reactions are suspected to be due to systemic Fucidin, treatment with systemic Fucidin should be stopped and it is recommended not to reintroduce the therapy.

Fusidic acid is metabolised in the liver and excreted in the bile. Elevated liver enzymes and jaundice have occurred during systemic Fucidin Leo therapy but are usually reversible on discontinuation of the drug.

Systemic Fusidin Leo should be given with caution and liver function should be monitored if used in patients with hepatic dysfunction or in patients taking potentially hepatotoxic drugs. Caution is required in patients with biliary disease and biliary tract obstruction. Caution is required in patients treated with HIV-protease inhibitors (see section 4.5). Fusidic acid competitively inhibits binding of bilirubin to albumin. Caution is necessary if systemic Fucidin Leo is administered to patients with

impaired transport and metabolism of bilirubin. Particular care is advised in neonates due to the theoretical risk of kernicterus.

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

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine due to the content of lactose.

This medicinal product contains 11mg sodium per tablet. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic Fucidin Leo with statins. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with Fucidin Leo is necessary, statin treatment should be discontinued throughout the duration of the Fucidin Leo treatment. Also see section 4.4.

Specific pathways of Fucidin metabolism in the liver are not known, however, an interaction between Fucidin and drugs being CYP-3A4 biotransformed can be suspected. The mechanism of this interaction is presumed to be a mutual inhibition of metabolism. There is insufficient data to characterise the effect of fusidic acid on CYPs *in-vitro*. The use of Fucidin systemically should be avoided in patients treated with CYP-3A4 biotransformed drugs.

<u>Oral anticoagulants</u>

Systemic Fucidin Leo administered concomitantly with oral anticoagulants such as coumarin derivatives or anticoagulants with similar actions may increase the plasma concentration of these agents enhancing the anticoagulant effect. Anticoagulation should be closely monitored and a decrease of the oral anticoagulant dose may be necessary in order to maintain the desired level of anticoagulation. Similarly, discontinuation of Fucidin may require the maintenance dose of anticoagulant to be re-assessed. The mechanism of this suspected interaction remains unknown.

HIV protease inhibitors

Co-administration of systemic Fucidin Leo and HIV protease inhibitors such as ritonavir and saquinavir may cause increased plasma concentrations of both agents which may result in hepatotoxicity.

Concomitant use is not recommended. (See section 4.4.)

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no or limited data (less than 300 pregnancy outcomes) from the use of fusidic acid in pregnant women. Animal studies do not indicate direct or indirect harmful effect with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of systemic Fucidin Leo during pregnancy.

Breast-feeding:

Physico-chemical data suggest excretion of fusidic acid in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from systemic Fucidin Leo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility:

There are no clinical studies with systemic Fucidin Leo regarding fertility. Pre-clinical studies did not show any effect of sodium fusidate on the fertility in rats.

4.7 Effects on ability to drive and use machines

Fucidin Leo has no or negligible influence on the ability to drive or to use machines.

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical trials and from spontaneous reporting.

The most frequently reported undesirable effects of Fucidin Leo administered orally are gastrointestinal disorders like abdominal discomfort and pain, diarrhoea, dyspepsia, nausea and vomiting. Anaphylactic shock has been reported.

Undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency group, adverse reactions are presented in the order of decreasing seriousness.

Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from available data)

Blood and lymphatic system disorders	
Uncommon	Pancytopenia Leukopenia[a)] Thrombocytopenia Anaemia
Immune system disorders	
Uncommon	Anaphylactic shock/anaphylactic reaction
Rare	Hypersensitivity
Nervous system disorders	
Uncommon	Headache Somnolence
Gastrointestinal disorders	
Common	Vomiting Diarrhoea Abdominal pain Dyspepsia Nausea Abdominal discomfort
Hepatobiliary disorders	
Uncommon	Hepatic failure

	Cholestasis Hepatitis[b)] Jaundice[c)] Hyperbilirubinaemia Liver function test abnormal[d)]
Rare	Hepatic function abnormal
Skin and subcutaneous tissue disorders	
Uncommon	Acute generalised exanthematous pustulosis Urticaria Pruritus Rash[e)] Erythema
Rare	Angioedema
Not known	Toxic epidermal necrolysis (Lyell´s syndrome)[f)] Stevens-Johnson syndrome [f)] Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome [f)]
Musculoskeletal and connective tissue disorders	
Uncommon	Rhabdomyolysis[g)]
Renal and urinary disorders	
Uncommon	Renal failure[h)]
General disorders and administration site conditions	
Common	Lethargy/Fatigue/Asthenia

a) Haematological disorders affecting the white cell line (neutropenia, granulocytopenia and agranulocytosis) have been reported.

b) Hepatitis also includes hepatitis cholestatic /cytolytic hepatitis

c) Jaundice also includes jaundice cholestatic

d) Including alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased and gamma glutamyltransferase

increased
e) Rash includes various types of rash reactions such as drug eruption, erythematous and maculo-papular rash
f) These adverse reactions were identified through post-marketing surveillance. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (see section 4.4)
g) Rhabdomyolysis may be fatal
h) Renal failure also includes renal failure acute.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults, based on limited data.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose
Acute symptoms of overdose include gastrointestinal disturbances. Management should be directed towards alleviation of symptoms. Dialysis will not increase the clearance of fusidic acid.
An overdose of 4 g/day for a duration of 10 days in an adult has been reported without any adverse events.
An overdose of 1,250 mg/day for a duration of 7 days in a child (3 years old) has been reported without any adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Steroid antibacterials, ATC code: J01XC01
Fusidic acid and its salts are potent anti-staphylococcal agents with unusual ability to penetrate tissue. Bactericidal levels have been assayed in bone and necrotic tissue.

Concentrations of 0.03-0.12 mcg/ml inhibit nearly all strains of *Staphylococcus aureus.*
Fusidic acid is active against *Staphylococcus epidermidis* and methicillin resistant staphylococci.

5.2 Pharmacokinetic properties

Blood levels are cumulative, reaching concentrations of 20-35 mcg/ml after oral administration of 250 mg twice daily for seven days and 50-100 micrograms/ml after oral administration of 500 mg three times daily for 3 to 4 days.
Fucidin Leo is excreted mainly in the bile, little or none being excreted in the urine.
In severe or deep-seated infections and when prolonged therapy may be required, Fucidin Leo should generally be given concurrently with other anti-staphylococcal antibiotic therapy.

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

Microcrystalline cellulose
Lactose monohydrate
Crospovidone
Talc
Hypromellose
Magnesium stearate
Silica colloidal anhydrous
All-rac-α-tocopherol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to store at room temperature.

6.5 Nature and contents of container

Aluminium/aluminium blisters. Pack sizes of 12, 36, 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

100-49-24510-00

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in November 2016 and updated according to the guidelines of the Ministry of Health in March 2020.