Fucidin®
Antistaphylococcal Antibiotic

Brand name
Fucidin®

Active ingredients and strength
Tablets: Sodium fusidate 250 mg

Presentation
The tablet is an approximately 7.8 x 16.0 mm white to off-white greyish marbled film-coated oval biconvex tablet without embossing.

Therapeutic properties
Properties: Fusidic acid is an antibiotic which mode of action is as inhibitor of the bacterial protein synthesis resulting in a bactericidal effect. Fusidic acid has a powerful antibacterial activity against a number of gram-positive microorganisms. Staphylococci, including the strains resistant to penicillin, methicillin or other antibiotics, are particularly susceptible to fusidic acid. Fusidic acid shows no cross-resistance to any other antibiotic agent used in clinical practice. Fucidin® tablets has an unusually good ability to penetrate tissue and is widely distributed in the organism. It is of great clinical importance that Fucidin® tablets provides high concentrations not only in areas well supplied with blood, but also in relatively avascular tissue. Concentrations exceeding the M.I.C. for Staphylococcus aureus (0.03-0.16 mcg/ml) have been found in pus, sputum, soft tissue, heart tissue, bone tissue, synovial fluid, sequestra, burn crusts, brain abscesses, and intraocularly. Fusidic acid is metabolized in the liver and mainly excreted through the bile, little or none being excreted through the urine.

Fucidin® tablets are generally atoxic and shows no crosshypersensitivity to other antibiotics in clinical use which is why Fucidin® tablets also can be used in many cases where other antibiotics are contraindicated, e.g. in patients allergic to penicillin or other antibiotics.

In severe or deep-seated infections and when prolonged therapy is required, Fucidin® tablets should generally be given concurrently with other antistaphylococcal antibiotic therapy to minimize the risk of resistance development. Fucidin® tablets may be combined with penicillinasestable penicillins, cephalosporins, erythromycin, aminoglycosides, lincomycin, rifampicin or vancomycin, and thus an additive or synergistic effect is obtained.

Indications
Fucidin® tablets are indicated for the treatment of infections caused by susceptible organisms, especially staphylococci, e.g. osteomyelitis, septicaemia, endocarditis, superinfected cystic fibrosis, pneumonia, skin and soft tissue infections, surgical and traumatic wound infections.

Dosage
Adults and children over 12 years: 500 mg (2 tablets) three times daily. Recommended dosage in skin and soft tissue infections: 250 mg sodium fusidate (1 tablet) twice daily. Dosage may be doubled in severe cases.

According to the metabolism and excretion of systemic Fucidin®, no dosage adjustment is needed in renal impairment or in patients undergoing haemodialysis as fusidic acid is not significantly dialysed.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Concomitant treatment with statins. See Special warnings and Precautions for use and Drug interaction.

Special warnings and Precautions for use
Statins (HMG-CoA reductase inhibitors) and systemic Fucidin® must not be co-administered. (see Contraindications) There have been reports of rhabdomyolysis (including fatalities) in patients receiving this combination. Statin treatment should be discontinued throughout the duration of treatment with systemic Fucidin®. 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®. 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® therapy but are usually reversible on discontinuation of the drug.

Systemic Fucidin® should be given with caution and liver function should be monitored if used in patients with hepatic dysfunction. Periodic liver function tests should be carried out in patients with liver dysfunction, abnormalities in the biliary pathway, when fusidic acid is given in high doses for prolonged periods, or when it is given in combination with other antibiotics which have similar excretion pathways, e.g. lincomycin and rifampicin. Caution is required in patients with biliary disease and biliary tract obstruction. Caution is required in patients treated with HIV-protease inhibitors (See Drug Interaction). Fusidic acid competitively inhibits binding of bilirubin to albumin. Caution is necessary if systemic Fucidin® 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine due to the content of lactose.

Interaction with other medicinal products and other forms of interaction

Statins (HMG-CoA reductase inhibitors)

Concomitant treatment with statins (HMG-CoA reductase inhibitors) is contraindicated. Co-administration of systemic Fucidin® and statins may cause possibly fatal rhabdomyolysis. Treatment with statins should therefore be discontinued throughout the duration of the treatment with systemic Fucidin®. Statin therapy may be reintroduced seven days after the last dose of systemic Fucidin®. (See Contraindications and Special warnings and Precautions for use)

Oral anticoagulants

Systemic Fucidin® administered concomitantly with oral anticoagulants such as coumarin derivatives or anticoagulants with similar actions may alter the anticoagulant effect. Adjustment of the oral anticoagulant dose may be necessary in order to maintain the desired level of anticoagulation.

HIV protease inhibitors

The use of Fucidin® systemic should be avoided in patients treated with CYP-3A4 biotransformed drugs.Co-administration of systemic Fucidin® and HIV protease inhibitors such as ritonavir and saquinavir may result in hepatotoxicity.
Concomitant use is not recommended. (See Special warnings and Precautions for use)

Other Interactions

Co-administration of Fucidin® systemic and cyclosporin has been reported to cause increased plasma concentration of cyclosporin.

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 reproductivity toxicity. As a precautionary measure, it is preferable to avoid the use of systemic Fucidin® 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® 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® regarding fertility. Pre-clinical studies did not show any effect of sodium fusidate on the fertility in rats.

Effects on the ability to drive and use machines

Fucidin® has no or negligible influence on the ability to drive or to use machines. However, patients should be informed about drowsiness that may occur during treatment and must consider it when driving or using machines.

Undesirable effects

Fucidin® tablets given orally may cause gastrointestinal disturbances (dyspepsia, nausea, vomiting)

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® 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 generalized exanthematous pustulosis Urticaria Pruritus Rash[e)] Erythema

Rare	Angioedema
Not known	Toxic epidermal necrolysis (Lyell's synfrome)[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 Special Warnings and Precautions for use).
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.

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 4g/day for a duration of ten days in an adult has been reported without any adverse events.
An overdose of 1,250 mg/day for a duration of seven days in a child (three years old) has been reported without any adverse events.

Pharmacological Properties
Pharmacodynamic properties
Pharmacotherapeutic group:Steroid Antibacterials, ATC code J01XC01
Sodium fusidate is an antibiotic, of steroid structure, belonging to the fusidanine group.

Pharmacokinetic properties
Absorption
Absorption is rapid following oral administration (by the 1st hour) and more than 90% of sodium fusidate is absorbed.

Distribution
Following single oral administration of 500 mg of sodium fusidate, maximum serum concentration is of the order of 30 mg/l on average at the 2nd hour. Mean serum half-life is 16 ± 3 hours.
Following repeated doses of 1.5 g/day, serum levels obtained gradually increase to reach steady state of between 50 and 100 mg/l, 8 hours after the last dose.
Ketofusidate, a metabolite which is only slightly active from a microbiological standpoint, is found in blood at levels equivalent to 10 to 15% of fusidic acid levels.

Humoral and tissue spread.
Half of all fusidic acid is found in the peripheral compartment, indicating that about 50% of fusidic acid is distributed in tissues.
It spreads through the majority of tissues, even those with a poor blood supply.
It is found in the skin (subcutaneous fat, crusts of burns), aseptic or infected bone (by way of an indication, mean levels in infected bone reach 7.5 µg/kg on the 8th day of treatment at the daily dosage of 1.5 g/day), in infected connective tissue, synovium, hepatobiliary secretions, bronchial secretions, mucus, the eye (aqueous humor or vitreous humor) and in pus regardless of the amount or its site (in particular intracranial pus).
Plasma protein binding is more than 90%.

Biotransformation
95% is excreted in inactive (metabolized) form in bile. Seven metabolites have been detected, three of which, accounting for about 30% of the total, still have antibacterial activity, though less than that of fusidic acid.

Excretion
Fusidic acid is mainly eliminated in bile and is subject to an enterohepatic cycle.
In contrast, urinary elimination is virtually nil, accounting for less than 1%.

Preclinical safety data
Not completed.

List of excipients
Microcrystalline cellulose, crospovidone(1), monohydrated lactose, magnesium stearate, anhydrous colloidal silica, talc, alpha-tocopherol, hypromellose, titanium dioxide.
The crospovidone is a synthetic homopolymer with crossed chains of N-vinyl-2 pyrrolidinone

Incompatibilites
Not applicable.

Storage condition
Do not store above 30°C.
Shelf life
Three years.
Pack Size
20 tablets (blister)
This leaflet was last revised in January 2018.
Manufactured by:
Laboratoires LEO

39, route de Chartres
28500 Vernouillet, France
For:
LEO Pharma A/S
Ballerup - Denmark