

DATA SHEET

Name of Medicine

FUCIDIN®

Sodium fusidate 250mg tablet
Sodium fusidate 500mg powder for injection

Presentation

Sodium fusidate is sodium (17Z)-16 β -acetoxy-3 α , 11 α -dihydroxyfusida-17(20),24-dien-21-oate; C₃₁H₄₇NaO₆; a white or almost white crystalline powder, slightly hygroscopic. The CAS number is 751-94-0. It is an antimicrobial substance produced by the growth of certain strains of *Fusidium coccineum*.

Uses

Actions

Pharmacology

Fusidic acid is a potent antibiotic derived from the fungus *Fusidium coccineum*.

Its mode of action is by inhibition of protein synthesis by the prevention of translocation on the ribosome. Concentrations adequate for bactericidal activity against staphylococci have been demonstrated in the following: pus, exudate, soft tissue, bone tissue, synovial fluid, aqueous humour, vitreous body, burn crusts, intracranial abscess, sputum, serum. Fusidic acid is structurally related to cephalosporin P and helvolic acid, neither of which has been developed for clinical use.

FUCIDIN® exerts antibacterial activity against most Gram-positive organisms; in particular, it is effective against pathogenic staphylococci, including penicillinase producing and methicillin-resistant strains. The MICs for most *Staph aureus* strains are between 0.02-0.12mg/L. It is much less active against *S. pyogenes* with the MIC between 4-20mg/L. It has slight or no activity against Gram-negative organisms and fungi.

Both oral and intravenous FUCIDIN® have been given in combination with other antibiotics, e.g. cloxacillin, cephaloridine, ampicillin, methicillin, erythromycin, novobiocin, rifampicin. Such a combination may prevent the development of FUCIDIN® resistant strains. No cross-resistance occurs between FUCIDIN® and any other antibiotic in clinical use. Because it is predominantly effective against Gram-positive organisms, disturbance of the normal gastrointestinal flora is unlikely.

Pharmacokinetics

FUCIDIN® is absorbed from the gastrointestinal tract producing maximum serum concentrations in 2 to 4 hours. Maximum serum levels (C_{max}), time to maximum serum concentration (T_{max}) and T_½ after an oral dose of 500mg sodium fusidate tablet are:

Under fed conditions: C_{max} of 31.76 µg/mL and T_{max} of 3.37 hours and T_½ 10.53 hours.

Under fasting conditions: C_{max} of 38.79 µg/mL and T_{max} 2.21 hours and T_½ 8.89 hours.

Following a single 250mg sodium fusidate tablet oral dose in fasting subjects, the mean C_{max} sodium fusidate was 11.6 µg/mL and the mean T_½ was reported to be 8.7 hours.

Accumulation also has been noticed after a dose of 500mg tds for four days. Absorption may be delayed by food, with a T_{max} of 2.21 hours under fasting conditions compared with 3.37 hours under fed conditions.. It is distributed into tissues and body fluids, including bone, pus and synovial fluid, but penetrates poorly to CSF. FUCIDIN[®] is bound to protein to a high degree (95%).

Only small amounts (on average only 0.15%) of FUCIDIN[®] is excreted in urine; it is mainly excreted and concentrated in bile. Approximately 2% is excreted in the faeces as the unchanged drug.

Indications

Treatment of localised as well as generalised staphylococcal infections (e.g. abscesses, furunculosis, wound infections, pneumonia, peritonitis, osteomyelitis, septicaemia, enteritis and otorhinolaryngeal infections).

Cystic fibrosis: FUCIDIN[®] is useful for elimination of staphylococci from the respiratory tract of patients with this condition.

Endocarditis: when the infecting organism has been shown to be susceptible.

If bacteriological diagnosis reveals methicillin-resistant *Staphylococcus aureus*, the use of FUCIDIN[®] monotherapy is not appropriate and concurrent treatment with other anti-staphylococcal antibiotics is necessary.

Dosage and Administration

Fucidin[®] tablets should be taken without a meal to avoid a reduction in the extent and rate of absorption of Fucidin[®] by a concomitant meal.

Oral tablets

- For community acquired mild to moderate acute skin and skin structure infections likely to be caused by methicillin – sensitive staphylococci e.g. boils, carbuncles, furuncles, superficial abscesses, paronychia, superficial wound infections and impetigo.

Adults 250mg twice daily

- For all other indications caused by *Staphylococcus aureus*.

Adults 2 x 250mg three times daily.

Children 5 to 12 years: 250mg three times daily.

Over 12 years: as for adults.

In severe infections, deep-seated infections, infections due to methicillin-resistant staphylococci or when prolonged therapy may be required, FUCIDIN[®] must be given concurrently with other anti-staphylococcal antibiotic therapy. Such combinations may produce enhanced activity, broaden the antibacterial spectrum and minimise the risk of less sensitive mutants. In general, full dosage of each antibiotic has been used and in severe infections, the dosage of FUCIDIN[®] may also be doubled.

The average duration of treatment is six days although more severe infection may indicate a longer period.

Dosage in Hepatic Insufficiency

Dosage reduction may be necessary in patients with hepatic impairment, since fusidic acid is cleared from the blood via hepatic metabolism.

Intravenous infusion (only)

Dissolve the dry substance in 10 mL of the buffer solution provided, dilute to 250 to 500 mL with Sodium Chloride injection, and infuse slowly over a period of not less than two to four hours.

Contains no antimicrobial preservative. To avoid the risk of microbial contamination, reconstituted solutions of sodium fusidate should be used as soon as possible after preparation.

Adults Usual dose: the contents of one vial three or four times daily by slow intravenous infusion. The dose of 2 g/day has been exceeded in a few cases.

Children A suggested dose is the equivalent of 20 mg/kg bodyweight of sodium fusidate daily, to be divided into three equal doses which should be given over a 24 hour period.

FUCIDIN[®] *must not* be administered intramuscularly or subcutaneously. FUCIDIN[®] should only be used suitably buffered and given as a slow infusion in a wide bore vein with a good blood flow. The dosage in patients undergoing haemodialysis needs no adjustment as FUCIDIN[®] is not significantly dialysed.

Contraindications

Concomitant treatment with statins, see **Interactions with other Medicines**

Patients with known hypersensitivity to fusidic acid and its salts or any excipient ingredient in the formulation of Fucidin[®].

Warnings & Precautions

Fucidin[®] must not be administered intramuscularly (IM) or subcutaneously because of high incidence of local tissue injury following IM route. Fucidin[®] Powder for Injection should only be used for IV infusion (see Dosage and administration)

Liver function tests should be performed regularly in patients taking high doses, in patients taking the drug for prolonged periods and in patients with abnormal liver function.

Risk-benefit should be considered when the following medical problems exist.

Hepatic function impairment: Fucidin[®] acid is metabolised in the liver; patients with impaired or immature hepatic function, especially neonates and infants or adults with impaired hepatic function, may require a reduction in dose or an alternative antibiotic should be considered.

Caution should be exercised if FUCIDIN[®] is administered with other drugs, including antibiotics (e.g. clindamycin and rifampicin), which have a similar biliary excretion pathway.

Fusidic acid and its salts, when administered systemically, and concomitantly with oral anticoagulants such as warfarin, other coumarin derivatives or anticoagulants with similar action, may increase the plasma concentration of these anticoagulant agents, enhancing the anticoagulant effect. Downward adjustment of the oral anticoagulant dose, monitored by laboratory coagulation testing and clinical status, may be necessary in order not to exceed the desired level of anticoagulation. The mechanism of this suspected interaction remains unknown.

Specific pathways of FUCIDIN[®] metabolism in the liver are not known, however, an interaction between FUCIDIN[®] and drugs biotransformed via CYP-3A4 is suspected. The apparent mechanism of this interaction is a mutual inhibition of metabolism. The use of FUCIDIN[®] systemically should be avoided in patients treated with CYP-3A4 biotransformed drugs. Common examples of CYP-3A4 biotransformed drugs are paracetamol, digitoxin and steroids.

Co-administration of systemic FUCIDIN[®] and HIV protease inhibitors, such as ritonavir and saquinavir, causes increased plasma concentrations of both agents, which may result in hepatotoxicity.

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

Resistance has developed both *in vitro* and *in vivo* and physicians should be alert to this possibility. In spite of the ease with which staphylococci develop resistance to FUCIDIN[®] *in vitro*, the development of resistance in clinical practice is not a frequent occurrence.

In animals, FUCIDIN[®] has a relatively low acute toxicity, the LD₅₀ for mice being 975 mg/kg bodyweight orally. Subacute and chronic toxicity tests in guinea pigs and rats showed no significant effects. In reproduction studies, mating frequency and fertility were normal and the offspring showed no morbid changes.

Use in Pregnancy: Category C

Fusidic acid may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Fusidic acid should be avoided when possible during the last month of pregnancy.

Use in Lactation

Safety in lactation has not been established. There is evidence that the drug can penetrate the placental barrier and is detectable in human milk. Caution is therefore required when FUCIDIN[®] is used in mothers who wish to breast feed.

Use in Neonates

FUCIDIN[®] has been given to neonates from the day of birth and for periods of up to one year without adverse effects. Despite the immature enzyme system in the neonate, none of the children showed any evidence of hepatotoxicity, nor did they develop renal, blood, ocular or other toxicity.

Effects on ability to drive and use machines

Sodium fusidate has no or negligible influence on the ability to drive and to use machines,

Adverse Effects

Gastrointestinal Reactions: Nausea, vomiting, epigastric pain, anorexia, diarrhoea and dyspepsia. The incidence of these effects with the oral presentations can be lessened by taking the medication with food. FUCIDIN[®] can cause disturbances of liver function including jaundice. Typically there is a predominant elevation of conjugated bilirubin. Elevations of alkaline phosphatase and transaminase levels are usually less marked. Recovery normally follows cessation of the use of FUCIDIN[®]. The incidence of jaundice is higher with intravenous therapy. In some instances where the onset of jaundice was associated with the intravenous use of FUCIDIN[®], recovery followed a change to oral therapy but this was not invariable.

Venospasm and thrombophlebitis have been observed with I.V. administration. Inflammation and redness at the infusion site have also been observed.

Skin rashes and pruritus have been observed on rare occasions. Dizziness, blurred vision and headaches have been generally mild and infrequent.

Leukopenia*, thrombocytopenia, pancytopenia and anaemia.

*Haematological disorders affecting the white cell line (neutropenia, granulocytopenia, agranulocytosis) and more rarely disorders affecting the other two cell lines have been reported,

either as isolated or associated events. This has been observed especially in cases of treatment duration of more than 15 days and is reversible upon drug withdrawal.

Musculoskeletal, connective tissue and bone disorders: Frequency not known: Rhabdomyolysis (examples of signs and symptoms are muscle weakness (swelling and pain), dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia), see **Interactions**.

Severe allergic reactions including angioneurotic oedema have been reported rarely.

Adverse events reported amongst patients treated with FUCIDIN® for staphylococcal skin infections at different dosage regimes during controlled clinical trials are shown in the table below. A dash represents an incidence of less than 1%.

	FUCIDIN® 250mg twice daily	FUCIDIN® 500mg twice daily	FUCIDIN® 500mg three times daily
Number treated	379	381	201
Number of patients with Adverse Drug Events (%)	58 (15.3%)	94 (24.7%)	50 (24.9%)
Nausea	14 (3.7%)	18 (4.7%)	24 (11.9%)
Vomiting	–	–	5 (2.5%)
Indigestion / Dyspepsia	–	14 (3.7%)	6 (3.0%)
Diarrhoea / loose stools	14 (3.7%)	30 (7.9%)	6 (3.0%)
Stomach / abdominal pain	11 (2.9%)	20 (5.3%)	8 (4.0%)
Flatulence	–	6 (1.6%)	2 (1.0%)
Headache	4 (1.0%)	–	3 (1.5%)
Lethargy	14 (3.7%)	12 (3.2%)	5 (2.5%)
Urticaria	–	7 (1.8%)	–

Interactions

Co-administration of systemic Fucidin® and HMG-CoA reductase inhibitors such as statins causes significantly increased plasma concentrations of both agents. This may result in an elevation of creatine kinase level and risk of rhabdomyolysis, muscle weakness and pain. Concomitant treatment with statins is therefore contraindicated, see **CONTRAINDICATIONS**.

Caution should be exercised with other antibiotics which may have similar biliary excretion pathways, e.g. clindamycin and rifampicin.

The intravenous infusion of fusidic acid is incompatible with acid solutions, with kanamycin, gentamicin, cephaloridine, and carbenicillin, and should not be diluted with glucose solution as precipitation may occur with the more acid samples.

FUCIDIN® should not be infused with amino acid solutions or whole blood because of the risk of haemolysis of erythrocytes.

Overdosage

Effects

Early symptoms may include epigastric or gastric discomfort and possibly diarrhoea. Prolonged ingestion of high doses may produce jaundice and other abnormalities of liver function.

Treatment

There are no published reports of the treatment of accidental massive overdosage with FUCIDIN[®] and there has been no experience with any specific treatment. Treatment should be restricted to symptomatic and supportive measures. Dialysis is of no benefit, because the drug is not significantly dialysed.

Pharmaceutical Precautions

Tablets	sodium fusidate 250mg: white, film-coated, ovoid
Intravenous infusion	1 vial contains sodium fusidate 500mg as a dry powder, the second vial contains 10mL sterile buffer solution (pH 7.4 to 7.6)

Tablets	Store below 30°C.
Powder for Injection	Store below 25°C.

Intravenous FUCIDIN[®] powder is stable for three years. Once brought into solution, it should be used within 24 hours.

Medicine Classification

Prescription Only Medicine

Package Quantities

FUCIDIN [®] tablets:	12 x 250mg tablets in a strip blister pack
FUCIDIN [®] intravenous infusion:	1 x vial; sodium fusidate 500mg and 1 x vial; buffer solution

Further Information

Excipients

FUCIDIN[®] powder for injection contains no excipients. The buffer solution contains disodium phosphate (dihydrate), citric acid (monohydrate), disodium edetate and water for injection.

FUCIDIN[®] tablets contain cellulose (microcrystalline), crospovidone, lactose, magnesium stearate, alpha-tocopherol, silica (colloidal anhydrous), talc (purified), hypromellose and titanium dioxide.

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