NEW ZEALAND DATA SHEET

1 FUCIDIN®

250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSTION

Each tablet contains active ingredient sodium fusidate 250 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet: white, film-coated, ovoid.

4 CLINICAL PARTICULARS

4.1 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.

4.2 Dosage and method of 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.

4.3 Contraindications

Concomitant treatment with statins (HMG-CoA reductase inhibitors), see section 4.5.

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

4.4 Special warnings and precautions for use

The medicinal product contains 0.45 mmol (11 mg) sodium per tablet, equivalent to 0.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fucidin® must not be co-administered with statins (HMG-CoA reductase inhibitors). There have been reports of rhabdomyolysis (including some 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 Fucidin® treatment. 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 Fucidin®.

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.

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: fucidic 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 is required in patients with biliary disease and biliary tract obstruction. 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.

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® is administered to patients with impaired transport and metabolism of bilirubin. Particular care is advised in neonates due to the theoretical risk of kernicterus (see Use in neonates section below).

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.

Resistance has developed both in vitro and in vivo and physicians should be alert to this possibility. As with all antibiotics, extended or recurrent use may increase the risk of developing antibiotic resistance.

In animals, Fucidin® has a relatively low acute toxicity, the oral LD_{50} for sodium fusidate in mice being 975 mg/kg bodyweight. Subacute and chronic toxicity tests in guinea pigs and rats showed no significant effects.

Use in Neonates
Fusidic acid may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin.

4.5 Interaction with other medicines and other forms of interaction

Concomitant treatment with statins (HMG-CoA reductase inhibitors) is contraindicated (see section 4.3). Co-administration of systemic Fucidin® and statins may cause possibly fatal rhabdomyolysis. Treatment with statins should therefore be discontinued throughout the duration of treatment with systemic Fucidin®. Statin therapy may be reintroduced after seven days after the last dose of systemic Fucidin®. Also see section 4.3 and 4.4.

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 alter the anticoagulant effect. Adjustment of the oral anticoagulant dose, monitored by laboratory coagulation testing and clinical status, may be necessary in order to maintain 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. Concomitant use is not recommended.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy: Category C

In reproduction studies, mating frequency and fertility were normal and the offspring showed no morbid changes. As a precautionary measure, it is preferable to avoid the use of systemic Fucidin® during

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.

4.7 Effects on ability to drive and use machines

Sodium fusidate has no or negligible influence on the ability to drive and 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® 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[1], thrombocytopenia, anaemia

Immune system disorders
Uncommon: Anaphylactic shock/anaphylactic reaction
Rare: Hypersensitivity

Nervous system disorders
Common: Headache
Uncommon: Somnolence

Gastrointestinal disorders
Common: Vomiting, diarrhoea, abdominal pain, dyspepsia, nausea, abdominal discomfort, flatulence

The incidence of these effects can be lessened by taking the medication with food.

Hepatobiliary disorders
Uncommon: Hepatic failure, cholestasis, hepatitis[2], jaundice[3], hyperbilirubinaemia, liver function test

[1] Haematological disorders affecting the white cell line (neutropenia, granulocytopenia and 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.

[2] Hepatitis also includes Hepatitis cholestatic /Cytolytic hepatitis

[3] Jaundice also includes Jaundice cholestatic

abnormal[4]
Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders
Common: Urticaria
Uncommon: Acute generalized exanthematous pustulosis, , rash[5], Rare: Angioedema, pruritus, erythema
Not known: Toxic epidermal necrolysis (Lyell´s syndrome)[6], Stevens-Johnson syndrome[6], Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome[6]

Renal and urinary disorders
Uncommon: Renal failure [7]

General disorders and administration site conditions
Common: Lethargy/Fatigue/Asthenia

Musculoskeletal and connective tissue disorders
Uncommon: Rhabdomyolysis (examples of signs and symptoms are muscle weakness (swelling and pain), dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia). Rhabdomyolysis may be fatal. See section 4.5.

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®

Dizziness, blurred vision and headaches have been generally mild and infrequent.

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

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 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.

For more information on the management of overdose or unintentional ingestion, contact the National Poisons Centre on 0800 **POISON** (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

Sodium fusidate is sodium (17Z)-16β-acetoxy- 3α, 11α -dihydroxyfusida-17(20),24-dien-21-oate;

[4] Including alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased and gamma-glutamyltransferase increased

[5] Rash includes various types of rash reactions such as drug eruption, erythematous and maculo-papular rash

[6] 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).

[7] Renal failure also includes renal failure acute

$C_{31}H_{47}NaO_6$; 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*.

5.1 Pharmadynamic properties

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 0.02-0.12 mg/L. It is much less active against *S. pyogenes* with the MIC between 4-20 mg/L. It has slight or no activity against Gram-negative organisms and fungi.

Oral Fucidin® has 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.

5.2 Pharmacokinetic properties

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 500 mg 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 250 mg 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 500 mg 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.

6 PHARMACEUTICAL PARTICULARS

6.1 Excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life
36 months

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
12 x 250 mg tablets in a strip blister pack
36 x 250 mg tablets in a strip pack

7 MEDICINE SHEDULE
Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL
Original formulation 31 Dec 1969
Reformulation 07 June 2007

10 DATE OF REVISION OF THE TEXT
27 April 2020

Summary Table of Changes

Section changed	Summary of new information
6.5	Addition of new pack size (36)
8	Update to sponsor details and removal of manufacturer