1. NAME OF THE MEDICINAL PRODUCT

FUCIDINE 250 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium fusidate.....250,0 mg

For one 502,4 mg film-coated tablet.

Excipient with known effect: lactose, sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FUCIDINE is indicated for the treatment of staphylococcal infections, especially in their cutaneous, osseous and articular manifestations.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults

1 to 1.5 mg/day, in two or three doses, depending on the severity of the staphylococcal infection treated. The serum fusidic acid concentrations obtained, and the normally low minimum inhibitory concentration of this antibiotic with respect to staphylococci, may allow the administration of fusidic acid at a lower dose with good therapeutic efficacy.

Children over 6 years of age

30 to 50 mg/kg/day, depending on the seriousness of the staphylococcal infection treated.

4.3 Contraindications

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

Concomitant treatment with statins (HMG-CoA reductase inhibitors). (See sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Special warnings

Concomitant treatment with statins (HMG-CoA reductase inhibitors) is contraindicated due to the increased risk of concentration-dependent undesirable effects of rhabdomyolysis type (see sections 4.3 and 4.5). Cases of death have occurred in patients treated with statins having received fusidic acid for osteoarticular infections. Treatment with the HMG-CoA reductase inhibitor should therefore be discontinued before and during the course of treatment with fusidic acid. Treatment with a statin may be reintroduced seven days after the last dose of Fucidine. If treatment with the HMG-CoA reductase inhibitor cannot be discontinued, an alternative antibiotic should be used.

The patient should be advised to seek medical advice immediately in case of muscle weakness, pain or tenderness.

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

As fusidic acid diffuses into the renal parenchyma but does not clear in the urine, treatment with fusidic acid is not suitable for the management of urinary tract infections.

Cases of bacterial resistance have been reported with the use of fusidic acid. Extended or recurrent use may increase the risk of antibiotic resistance.

Special precautions for use

Fusidic acid is metabolised in the liver and excreted in the bile. Elevated liver enzymes and jaundice may occur during Fucidine therapy, but are usually reversible on discontinuation of the drug. In case of hepatic impairment, Fucidine should be administered with caution and liver function monitored. Patients with biliary disease and biliary tract obstruction should be treated with caution.

Fusidic acid competitively inhibits binding of bilirubin to albumin. Caution is necessary if Fucidine is administered to patients with impaired transport and metabolism of bilirubin. Particular care is advised in neonates due to the theoretical risk of kernicterus.

Caution is required in patients treated with HIV-protease inhibitors (see section 4.5).

This medicinal product contains 0,48 mmol (11 mg) sodium per tablet, equivalent to 0,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a strict low sodium diet.

This medicinal product contains lactose. Its use is advised against in patients with galactose intolerance, Lapp lactase deficiency, or glucose or galactose malabsorption syndrome (rare hereditary diseases).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

HMG-CoA reductase inhibitors

Increased risk of concentration-dependent undesirable effects such as rhabdomyolysis (see sections 4.3 and 4.4). Stop treatment with the HMG-CoA reductase inhibitor before starting treatment with fusidic acid, or use an alternative antibiotic.

Combinations requiring precautions for use

Ciclosporin

Risk of increase of blood concentrations of ciclosporin and of creatininaemia. Monitoring of blood ciclosporin concentrations, control of renal function and dose adjustment are recommended during treatment and after discontinuation.

Combinations to be taken into account

HIV protease inhibitors

Co-administration of Fucidine 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).

Anti-infectious agents and INR

Several cases of vitamin K antagonist activity increase have been reported in patients receiving antibiotics treatment. Any marked inflammatory condition or underlying infection, and the age and general condition of the patient appear to be risk factors. Under these circumstances, it is difficult to distinguish the between the infectious pathology and its treatment in the onset of the INR imbalance. However, certain classes of antibiotics are more implicated than others: those include fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins which, under these conditions, make reinforced surveillance of the INR necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown no evidence of direct or indirect harmful effects on reproduction. Data concerning the use of fusidic acid in pregnant women are limited.

Due to the expected therapeutic benefit, use of fusidic acid may be considered during pregnancy if required, despite the limited clinical data.

Breast-feeding

Data suggest that fusidic acid may pass into breast milk. As a precautionary measure, you should not use fusidic acid during breast-feeding.

Fertility

No clinical studies on the effects of topical Fucidine on fertility have been conducted. Preclinical studies in rats did not show any effect of fusidic acid on fertility.

4.7 Effects on ability to drive and use machines

Fucidine has no or negligible influence on the ability to drive and use machines.

However, patients should be advised that drowsiness may occur during treatment, which should be taken into consideration when driving or using machinery.

4.8 Undesirable effects

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

The most frequently reported undesirable effects of Fucidine administered orally are gastrointestinal disorders such as abdominal discomfort and pain, diarrhoea, dyspepsia, nausea and vomiting. Anaphylactic shocks have been reported.

Undesirable effects are listed by MedDRA System Organ Class (SOC) starting with the most common. Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Very common (≥ 1/10)

Common (≥ 1/100, < 1/10)

Uncommon (≥ 1/1,000, < 1/100)

Rare (≥ 1/10,000, < 1/1,000)

Very rare (< 1/10,000)

Frequency not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Uncommon	Pancytopenia, neutropenia, agranulocytosis, thrombocytopenia, anaemia including sideroblastic anaemia[(a)]
Immune system disorders	
Rare	Hypersensitivity
Frequency not known	Immediate or delayed hypersensitivity reactions (including angioedema, anaphylactic/anaphylactoid shock)
Nervous system disorders	
Uncommon	Headache, somnolence
Gastrointestinal disorders	
Common	Gastrointestinal disorders, especially dyspepsia, vomiting, diarrhoea, abdominal pain
Hepatobiliary disorders	
Common	Hyperbilirubinaemia, jaundice
Frequency not known	Cytolytic, mixed or cholestatic hepatitis, abnormalities in liver function tests including increased alanine aminotransferase, aspartate aminotransferase and blood alkaline phosphatase
Skin and subcutaneous tissue disorders	
Uncommon	Rashes of various types, especially maculopapular and erythematous rash, urticaria
Rare	Angioedema Pruritus Erythema
Frequency not known	Generalised acute exanthematous pustulosis, vascular purpura, toxic epidermal necrolysis (Lyell syndrome)[(b)], Stevens-Johnson syndrome[(b)], Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome)[(b)]
Musculoskeletal and connective tissue disorders	
Frequency not known	Rhabdomyolysis[(c)]
Renal and urinary disorders	
Uncommon	Renal failure[(d)]
General disorders and administration site conditions	
Common	Lethargy/fatigue/asthenia

[(a)]Haematological disorders have been observed more particularly in cases of treatment lasting more than 15 days.

[(b)]These undesirable effects have been identified during post-marketing surveillance. Since these effects have been reported spontaneously in a population of unknown size, it is not possible to reliably estimate their frequency (see section 4.4).

[(C)]Rhabdomyolysis, mainly when co-prescribed with an HMG-CoA reductase inhibitor. See sections 4.3, 4.4 and 4.5.

[(d)]Renal failure includes acute renal failure.

Paediatric population

Frequency, type and severity of undesirable effects 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. Healthcare professionals are asked to report any suspected adverse reactionsvia the national reporting system: Agence nationale de sécurité du médicament et des produits de santé (French National Agency for the Safety of Medicines and Health Products - ANSM) and the network of Regional Pharmacovigilance Centres – Website: www.ansm.sante.fr.

4.9 Overdose

Acute symptoms of overdose include gastrointestinal disorders. Treatment is symptomatic. Dialysis does not increase the clearance of fusidic acid. An overdose of 4 g per day for a duration of ten days has been reported in an adult without any adverse event. An overdose of 1250 mg/day for a duration of seven days in a child (3 years old) has been reported without any adverse event.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: STEROID ANTIBACTERIALS, ATC code: J01XC01.

Sodium fusidate is a steroidal antibiotic belonging to the fusidanin group.

SPECTRUM OF ANTIBACTERIAL ACTIVITY

Critical concentrations separate susceptible strains from strains of intermediate susceptibility, and the latter from resistant strains:

S ≤ 2 mg/l and R > 16 mg/l

The prevalence of acquired resistance can vary geographically and temporally for certain species. It is therefore useful to have information on the prevalence of local resistance, particularly for treating severe infections. These data can only provide guidance on the probabilities of the susceptibility of a bacterial strain to this antibiotic. Where the variability of prevalence of resistance in France is known for a bacterial species, it is indicated in the following table:

Categories	**Frequency of acquired resistance in France (> 10 %) (extreme values)**
SUSCEPTIBLE SPECIES **Gram-positive aerobes** *Staphylococcus aureus* *Staphylococcus non-aureus* **Anaerobes** *Clostridium difficile* *Clostridium perfringens* *Peptostreptococcus* *Propionibacterium acnes*	5–20%
MODERATELY SUSCEPTIBLE SPECIES (*in vitro* intermediate susceptibility) **Gram-positive aerobes**	

Streptococcus	
RESISTANT SPECIES **Gram-negative aerobes** *Acinetobacter* *Enterobacteria* *Pseudomonas*	

5.2 Pharmacokinetic properties

Absorption

Following oral administration, absorption is rapid (from the first hour), and more than 90% of sodium fusidate is absorbed.

Distribution

Following a single 500 mg fusidate sodium oral dose, maximum serum concentrations mean are of the order of 30 mg/l, as of the second hour. The mean serum elimination half-life is 16 + 3 hours.

Following repeated doses of 1,5 g/day, serum concentrations increase gradually up to a balance of 50 to 100 mg/l, 8 hours after the last dose.

A weak bacteriologically active metabolite, keto-fusidate is found in the blood at levels representing 10–15% of the fusidic acid concentration.

Humoral and tissue diffusion

Half of the fusidic acid is found in the peripheral compartment, which means that about 50% is distributed in the tissues.

It diffuses into most tissues, even poorly vascularised tissues.

It is found in the skin (subcutaneous fat, burn scabbing), aseptic or infected bone (for reference, in the infected bone, concentration mean is 7,5 mg/g on day 8 of treatment at a dose of 1,50 g/day), infected connective tissue, synovium, hepatobiliary secretions, bronchial secretions, mucus, eye (aqueous humor and vitreous humor), pus whatever the quantity of the purulent collection or its location (but especially in intracranial pus).

Plasma protein binding is greater than 90 percent.

Biotransformation

In the bile, 95% is excreted in inactive (metabolised) form: seven metabolites have been detected, of which three, representing 30% of the total, have some residual antibacterial activity, weaker than that of fusidic acid.

Elimination

Fusidic acid is primarily excreted in the bile and undergoes an enterohepatic cycle.

However, urinary elimination is practically nil. Urinary elimination represents less than 1% of the total.

5.3 Preclinical safety data

Not documented.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, crospovidone[(1)], lactose monohydrate, magnesium stearate, anhydrous colloidal silica, talc, alpha tocopherol, hypromellose, titanium dioxide.

[(1)]Crospovidone is a synthetic cross-linked homopolymer of N-2-vinylpyrrolidinone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Boxes of 10 or 100 tablets in blister packs (PVC-PVDC/Aluminium).

Boxes of 10 or 100 tablets in blister packs (PVC/Aluminium/Aluminium).

Boxes of 10 or 100 tablets in blister packs (Aluminium/Aluminium).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRES LEO
2 RUE RENE CAUDRON
78960 VOISINS LE BRETONNEUX
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 332 192 8 4: 10 tablets in blisters (PVC-PVDC/Aluminium).
- 34009 558 357 8 3: 100 tablets in blisters (PVC-PVDC/Aluminium).
- 34009 364 975 8 0: 10 Tablets in blister packs (Aluminium/Aluminium/PVC).
- 34009 565 468 6 2: 100 Tablets in blister packs (Aluminium/Aluminium/PVC).
- 34009 367 663 7 2: 10 Tablets in blister packs (Aluminium/Aluminium).
- 34009 565 881 0 7: 100 Tablets in blister packs (Aluminium/Aluminium).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed by the holder]

10. DATE OF REVISION OF THE TEXT

[to be completed by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I