

PRODUCT MONOGRAPH

PrFUCIDIN®

Fusidic acid
2% Cream

Sodium fusidate
2% Ointment

Antibiotic

LEO Pharma Inc.
Thornhill, Ontario
L3T 7W8
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August 6, 2008

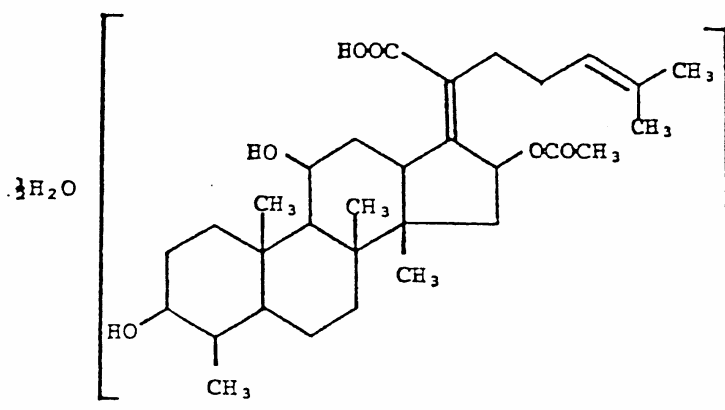
Variation No.: 01

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STRUCTURAL FORMULA AND CHEMISTRY

Fusidic Acid Hemihydrate



Molecular Formula: $\text{C}_{31}\text{H}_{48}\text{O}_6 \cdot 1/2\text{H}_2\text{O}$

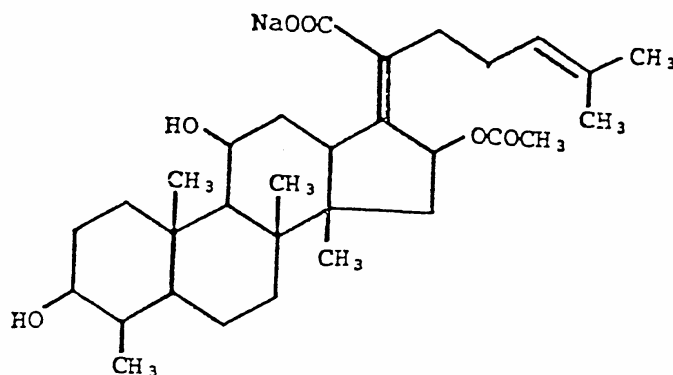
Molecular Weight: 525.7

Chemical Name: *ent*-(17*Z*)-16 α -(Acetyloxy)-3 β ,11 β -dihydroxy-4 β ,8,14-trimethyl-18-nor-5 β ,10 α -cholesta-17(20),24-dien-21-oic acid hemihydrate

Description: White crystalline powder, insoluble in water.

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Sodium Fusidate:



Molecular Formula: C₃₁H₄₇NaO₆

Molecular Weight: 538.7

Chemical Name: Sodium (*Z*)-*ent*-16 α -(acetyloxy)-3 β ,11 β -dihydroxy-4 β ,8,14-trimethyl-18-nor-5 β ,10 α -cholesta-17(20),24-dien-21-oate

Description: Sodium fusidate is a white crystalline powder, soluble in one part of water at 20°C.

NAME OF DRUG

PrFUCIDIN®

Fusidic acid, 2% Cream

Sodium fusidate, 2% Ointment

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

The antibacterial action of fusidic acid results from the inhibition of bacterial protein synthesis. The drug interferes with amino acid transfer from aminoacyl-sRNA to protein on the ribosomes. Fusidic acid may be bacteriostatic or bactericidal depending on inoculum size. Although bacterial cells stop dividing almost within two minutes after contact with the antibiotic *in vitro*, DNA and RNA synthesis continue for 45 minutes and 1-2 hours, respectively.

FUCIDIN (fusidic acid) is virtually inactive against Gram-negative bacteria. The differences in activity against Gram-negative and Gram-positive organisms are believed to be due to a difference in cell wall permeability.

Mammalian cells are much less susceptible to inhibition of protein synthesis by FUCIDIN than sensitive bacterial cells. These differences are believed to be due primarily to a difference in cell wall permeability.

INDICATIONS AND CLINICAL USE

For use in the treatment of primary and secondary skin infections caused by sensitive strains of Staphylococcus aureus, Streptococcus spp and Corynebacterium minutissimum. Primary skin infections that may be expected to respond to treatment with FUCIDIN OINTMENT (sodium fusidate) and CREAM (fusidic acid) include: impetigo contagiosa, erythrasma and secondary skin infections such as infected wounds and infected burns.

Appropriate culture and susceptibility studies should be performed. However, while waiting results of these studies and, if antibiotic therapy is considered to be necessary, FUCIDIN OINTMENT and CREAM may be administered to those patients in whom an infection caused by susceptible bacteria is suspected. This antibiotic treatment may subsequently require modification once these results become available.

In addition, local concentrations of FUCIDIN OINTMENT and CREAM are active against other Corynebacteria spp, Neisseria spp, Clostridia spp and Bacteroides spp. No cross-resistance has been observed to date between FUCIDIN and other antibiotics presently in clinical use.

Resistance to FUCIDIN has readily been induced *in vitro*. The development of resistance has also been shown to occur in the clinical setting.

CONTRAINDICATIONS

Sensitivity to fusidic acid and its salts or with respect to FUCIDIN OINTMENT (sodium fusidate), sensitivity to lanolin.

PRECAUTIONS

Treatment of severe or refractory skin lesions should be supplemented with the administration of a systemic antibacterial agent. Use of topical antibiotics occasionally allows overgrowth of non-susceptible organisms. If this occurs, or irritation or sensitization develops, treatment with FUCIDIN OINTMENT (sodium fusidate) or CREAM (fusidic acid) should be discontinued and appropriate therapy instituted. FUCIDIN OINTMENT or CREAM should not be used in or near the eye because of the possibility of conjunctival irritation.

Use in Pregnancy

The safety of FUCIDIN in the treatment of infections during pregnancy has not been established. If the administration of FUCIDIN to pregnant patients is considered to be necessary, its use requires that the potential benefits be weighed against the possible hazards to the foetus. There is evidence to suggest that the drug can penetrate the placental barrier and that FUCIDIN is detectable in the milk of nursing mothers. The safety of FUCIDIN for the treatment of infections in women who are breastfeeding has not been established.

ADVERSE EFFECTS

In patients with dermatoses treated with FUCIDIN OINTMENT (sodium fusidate), mild irritation that did not usually require discontinuance of therapy has been occasionally reported. The application of FUCIDIN OINTMENT to deep leg ulcers has been associated with pain. Reports of hypersensitivity reactions have been rare.

DOSAGE AND ADMINISTRATION

A small amount of FUCIDIN OINTMENT (sodium fusidate) or CREAM (fusidic acid) should be applied to the lesion 3 or 4 times daily until favourable results are achieved. Whenever the lesion is to be covered with a gauze dressing, less frequent applications (1 or 2 daily) may be used. In impetigo contagiosa, it has not been shown necessary to remove the crusts before application of FUCIDIN OINTMENT or CREAM.

When required, incision and drainage of infected skin lesions should be carried out before treatment with FUCIDIN OINTMENT or CREAM.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage has not been known to occur during topical therapy with FUCIDIN OINTMENT (sodium fusidate) or CREAM (fusidic acid).

AVAILABILITY

FUCIDIN OINTMENT contains 2% sodium fusidate (1.92% fusidic acid as the sodium salt) in an ointment base containing lanolin. Available in tubes of 15 g and 30 g. Store between 15-30 °C.

FUCIDIN CREAM contains 2% fusidic acid in a cream base. Available in tubes of 15 g and 30 g. Store between 15-25 °C.

MICROBIOLOGY

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In Vitro Studies

FUCIDIN (fusidic acid) is active in vitro against Gram-positive bacteria and Neisseria species, but has almost no antibacterial activity against Gram-negative organisms. The in vitro susceptibility against a range of clinical isolates is illustrated in Table 1.

In vitro sensitivity to FUCIDIN can be determined by the Kirby-Bauer disc diffusion methods using discs containing 10 ug sodium fusidate.

N.B.: It is important to note that this sensitivity test is invalid if blood is present on the agar medium employed as FUCIDIN becomes bound to protein, even in the presence of a very small amount of blood.

The following criteria have been recommended for interpreting the results for Staphylococcus aureus:

Sensitive Organisms

Zone equal to or greater than 20 mm diameter (equivalent to an M.I.C. of 2 ug/mL or less).

Resistant Organisms

Zone equal to or less than 19 mm diameter. Streptococcal isolates showing inhibition zones of 12-18 mm diameter may be considered as sensitive to FUCIDIN OINTMENT (sodium fusidate) or CREAM (fusidic acid).

Table 1. Spectrum of *In Vitro* Activity of Sodium Fusidate

Species	No. of strains tested	Cumulative percentage of strains inhibited by given concentration of Fucidin (in ug/mL)**										Activity Range in ug/mL	
		0.015	0.03	0.06	0.12	0.25	0.5	1	2*	4	8		
Staph. aureus (penicillin sens.)	149	-	11	50	74	98	100	100	100	100	100	100	0.03 - 0.3
Staph. aureus (penicillin resist.)													
Strep. pyogenes	10	-	-	-	-	-	-	-	-	-	40	100	4 - 16
Strep. pneumoniae	13	-	-	-	-	-	-	-	-	8	46	100	2 - 16
Strep. faecalis	8	-	-	-	-	-	-	13	13	100	100	100	1 - 8
N. gonorrhoeae	102	-	9	19	30	47	76	92	96	99	100	100	0.03 - 4
N. meningitidis	108	18	51	81	92	98	100	100	100	100	100	100	0.015 - 0.5
Clostridium spp.	42	-	-	21	50	74	88	100	100	100	100	100	0.06 - 1.0
Peptostrep. spp.	15	-	-	13	40	67	73	93	100	100	100	100	0.06 - 2
Bacteroides fragilis	83	-	-	-	-	1	4	31	80	89	94	94	0.25 - 16
Bacteroides spp.	72	-	-	7	14	29	47	60	79	90	94	94	0.06 - 16
Corynebacterium spp.	118	-	-	77	79	-	-	87	-	98	-	-	0.06 - 12.5

* isolates with MIC's greater than 2 ug/mL are considered to be insensitive at those serum concentrations achievable with normal doses of Fucidin.
** Expressed as sodium fusidate

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The possibility of synergism between sodium fusidate and other antibiotics has been tested in meat infusion broth inoculated with sensitive strains of Staphylococcus aureus. Synergism has been demonstrated with penicillin V, penicillin G, erythromycin and picromycin.

In another experiment, the M.I.C.'s of combinations of benzyl penicillin or methicillin with fusidic acid were determined by the serial-dilution tube titration method. When the penicillin was added 2 hours before fusidic acid, the combination was synergistic. However when penicillin was added at the same time or later than fusidic acid, the two agents acted antagonistically. It has been suggested that these apparently opposing effects occur because fusidic acid rapidly inhibits protein synthesis, but the action of penicillin requires active cell growth. FUCIDIN and methicillin act antagonistically against staphylococcal strains which are susceptible to methicillin but not in methicillin-resistant strains.

Synergism between the penicillins and fusidic acid has only been observed with strains of Staphylococcus aureus that produce small amounts of penicillinase and not with penicillinase-stable penicillins.

In Vivo Studies

Mice Protection: Sodium fusidate, administered orally at levels of 20 to 2500 mcg per dose was tested in vivo in mice infected with a penicillin-resistant strain of Staphylococcus aureus, Streptococcus pyogenes C 203 or Mycobacterium tuberculosis, var. bovin, strain Ravenel. Sodium fusidate was active against Staphylococcus aureus at all levels, but active against Streptococcus pyogenes C 203 only at levels of 313 mg/dose and above. The drug did not prolong survival times of mice infected with Mycobacterium tuberculosis.

In another study, groups of mice were infected intraperitoneally with Streptococcus pyogenes C 203, Staphylococcus aureus (penicillin-resistant and penicillin-sensitive) or Diplococcus pneumoniae SV.1. When 1 dose of 250 mg/kg sodium fusidate was administered orally 24 or 6 hours prior to the staphylococcal infection, it protected 60% and 80% of the mice treated, respectively. When the single dose of sodium fusidate was administered 4, 2 and 1 hour pre-infection or at the time of

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infection, 100% of the mice were protected. Sodium fusidate administered subcutaneously failed to protect the mice against Streptococcus pyogenes C 203 and Diplococcus pneumonia infections, regardless of the time of administration. Single subcutaneous and oral doses of sodium fusidate, vernamycin B and erythromycin (4.0, 20.0 and 100 mg/kg) were tested in corticosterone-treated mice which had been infected intradermally with 2 strains of Staphylococcus aureus, all three drugs protected the animals from lesions with the 20 mg/kg s.c. dose when given one hour after infection. When administered subcutaneously one hour pre-infection, erythromycin was 5 times more active.

With the oral route, all three drugs provided complete protection with 100 mg/kg given at the time of infection, but 500 mg/kg or more was required when the drugs were administered 3 to 6 hours post-infection. When the same three drugs were tested against an intraperitoneally-induced staphylococcal infection, erythromycin was the most active drug.

Rabbit Protection: Rabbits were inoculated intradermally for 3 days with two different strains of Staphylococcus. When infection was induced 24 hours before the administration of sodium fusidate (32.5, 125 or 500 mg/kg), no beneficial effects on the induced lesions were observed; however, when the staphylococcal lesions were produced at the same time or 24 hours following drug administration, erythema was limited and the size of the lesions remained constant throughout the test period (1 week) for all dose levels.

Resistance in vivo

Although resistance to FUCIDIN has been rapidly induced in vitro, resistant strains have only occasionally been observed in the clinical setting. In one study, only 3 out of 1025 naturally occurring strains of Staphylococcus aureus were found to be resistant to FUCIDIN. In another study, only 10 out of 2700 clinical isolates of Staphylococcus showed resistance to FUCIDIN and all 10 strains were coagulase-positive Staphylococci. The degree of resistance exhibited by these strains was comparable to the resistance shown by various mutants in vitro.

Resistant strains of Staph. aureus have emerged following systemic treatment with FUCIDIN. In one study resistant strains of Staph. aureus emerged in 6 of 13 burn patients treated with 500 mg

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FUCIDIN two or three times daily for 7 days.

PHARMACOLOGY

FUCIDIN (fusidic acid) shows strong surface activity and is also fat soluble (Stewart, 1964). Using titriated FUCIDIN OINTMENT (sodium fusidate), Hart (1978) demonstrated the systemic absorption of the OINTMENT applied to the shaved backs of rabbits. Pre-treatment with 1% sodium lauryl sulfate in petroleum jelly increased absorption by from 0.02% to 0.16% to 0.2% to 3.4%. Vickers (1969) using excised human skin demonstrated penetration by fusidic acid and by sodium fusidate comparable to that seen with glucocorticoids. This was later confirmed by Knight (1969). In 1968, Kjelstrup demonstrated the penetration and accumulation of FUCIDIN in subcutaneous infected tissue in cases of atheromas. Penetration has also been demonstrated in the skin of an amputated finger, as well as in treated fingers and in bone periosteum.

TOXICOLOGY**Acute Toxicity**

The following Table summarizes the acute toxicity data obtained for mice and rats:

DRUG FORM TESTED	SPECIES	ROUTE OF ADMINISTRATION	NO. OF ANIMALS	LD₅₀ (mg/kg)
Sodium fusidate	Mouse	Oral	-	975
	Mouse-M	Oral	50	2150
	Mouse-M	Oral	190	2045
	Mouse-F		115	2100
	Mouse	Subcutaneous	-	313
	Mouse	Intravenous	-	205
	Mouse-M	Intravenous	80	180
	Mouse-F	Intravenous	175	190
	Mouse-M		90	175
	Mouse	Intraperitoneal	-	170
	Rat	Oral	11	2700
Fusidic acid	Mouse	Oral	-	5400
	Mouse	Intraperitoneal	-	355
	Rat Adults	Oral	10	2263
	Rat Pups		10	443
Diethanolamine	Mouse	Intravenous	10	232
Fusidate	Rat	Intravenous	10	192

The signs and symptoms of toxicity of fusidic acid and its salts in mice were decreased activity, ataxia and convulsions; in rats, the only symptoms preceding death were decreased activity and slight salivation.

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Dogs: Sodium fusidate was administered as a 10% solution by stomach tube to 2 fasted dogs in single doses of 250 and 500 mg/kg, respectively. Two other fasted dogs received the drug in the form of gelatin capsules in doses of 500 and 1500 mg/kg, respectively.

No effects were noted in the dogs receiving 500 mg/kg by capsules. The remaining 3 dogs vomited within 8 to 60 minutes; the dog given 1500 mg/kg was lethargic for 12 hours, but no other effects were observed during a 7 day observation period. A dose-dependent increase in BSP retention times was observed.

Subacute Toxicity

Rats: Sodium fusidate was administered in the diet of 2 groups composed of 5 male and 5 female rats at doses of 0 or 270 mg/kg/day for 4 weeks. A similar group received 500 mg/kg/day for 1 week and subsequently 1200 mg/kg/day for 3 weeks. None of the animals died during testing and no significant lesions attributable to the drug were found. Except for a slight to moderate weight retardation in males in the high dose group, the average rates of growth of the treated animals were comparable to those of the controls.

Dogs: Sodium fusidate was administered in the diet of 3 groups of 2 dogs each. One group served as the control; another group was dosed at 110 mg/kg/day for 4 weeks and the third group at 250 mg/kg for 1 week followed by 470 mg/kg/day for the next 3 weeks. None of the dogs showed any significant gross or micropathological alterations which were considered to be drug-related.

During the second and third weeks, one of the 2 dogs on the low dose showed reduction in appetite which was apparently due to poor palatability of the drug. One of the 2 dogs showed a slight weight loss. In the high dose group reductions in appetite limited drug intake to an average of 470 mg/kg/day. Both these animals had small weight losses, probably associated with reduced food intake.

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Chronic Toxicity

Rats: Sodium fusidate was administered in the diet to 4 groups of 40 rats at doses of 0, 200, 420 or 840 mg/kg daily for 34 weeks. High dose females and to a lesser degree, high dose males showed a small retardation of weight gain. Slight neutrophilia was also noted in both high dose males and females. Ten of the 14 high dose males showed mild fatty metamorphosis of the liver without significant cytopathological change.

In another study, rats received sodium fusidate administration orally at a dose of 200 mg/kg/day for 24 weeks. No influence on growth or hematology and no other toxic effects were observed.

In a third study, fusidic acid was administered orally to a group of 25 male and 25 female rats at a dose of 400 mg/kg/day, 6 days a week for 5 months. No hematological changes or other toxic effects were noted.

Guinea Pigs: No toxic effects were seen when sodium fusidate was administered orally to guinea pigs at doses of 80 mg/kg/day for 50 days.

Dogs: Sodium fusidate was included in the diet of 4 groups of 5 dogs in amounts to result in doses of 0, 90, 190 or 300 mg/kg for 26 weeks. Significant changes observed were: weight loss with significantly reduced appetite in one animal on the high dose; however, all other test animals maintained or gained weight comparable to the control group in spite of slightly reduced food intake ascribed by the investigator to poor palatability; one dog on the high dose showed definite increases in plasma bilirubin and BSP; one dog on the intermediate dose showed slight to moderate increases in BSP, SGPT and alkaline phosphatase; one dog on the low dose showed a moderate increase in alkaline phosphatase and a slight increase in plasma bilirubin.

In another study, post-mortem examination revealed mild to moderate liver cell damage in one high dose dog (400 mg/kg/day) at 26 weeks, but the other animals showed no morphological changes with this dose attributable to the drug.

Fertility and Reproduction Studies

Two groups, each comprised of 20 male and 20 female rats, received either 0 or 400 mg/kg sodium fusidate per day for 2 weeks before mating to weaning. Caesarian sections were performed on half the dams on the 20th day; the remainder were allowed to deliver naturally.

There were no significant differences between the treated and control dams with respect to per cent resorptions, the condition of the uteri or the number and weights of the pups. No soft tissue abnormalities were found in the pups of either group but skeletal anomalies (control group 2 pups missing ribs and dosed group 1 pup occipital bone formation incomplete and 1 pub rib deformities) appeared in 4% of the pups in both groups. The viability and lactation indices, reflecting neonatal development, were higher in the treated group than the control group, but all values were within normal limits.

Teratology Studies

Mice: Pregnant mice were divided into 3 groups of 16-19 animals each and given daily doses of 20, 100 and 200 mg/kg sodium fusidate by gavage from the 6th to 15th day of gestation. Another group of 23 pregnant mice, serving as controls, received just water by gavage. On the 18th day of pregnancy, half the dams were sacrificed. The remainder was allowed to go to term.

Sex distribution of fetuses and young, fetal weight, birth weight and weight increase were normal and similar for all groups. The mean incidence of resorption was 1.2, 1, 0.5 and 0.6 per dam for the 20, 100 and 200 mg/kg groups and control group, respectively. Average litter size in the treated group did not differ significantly from that of the controls in any of the groups.

Rats: Pregnant rats were divided into 3 groups of 29-31 animals each and given daily doses of 20, 100 or 200 mg/kg sodium fusidate by gavage from the 3rd to the 15th day of gestation. Another group of 59 pregnant rats, serving as controls, received just water by gavage. On the 21st day of pregnancy, half the dams were sacrificed. The remaining dams were allowed to go to term.

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The average rate of resorption was 1.2, 1.8, 1.7 and 1.3 per dam for the 20, 100 and 200 mg/kg and control groups, respectively. Litter size and sex distribution of the fetuses and young of the dosed animals were comparable to the controls with no dose-related differences. Birth weights and weight gain over a 4 month period were comparable for all groups. No fetal deformities were observed in any group.

Rabbits: Eighteen pregnant rabbits were treated orally with 125 mg sodium fusidate in tablet form once per day from the 6th to the 18th day of pregnancy. Eleven pregnant animals, serving as controls, received a placebo tablet each day. On the 30th day of pregnancy 9 treated animals and 3 controls were sacrificed. The remaining animals were allowed to go to term.

Sex distribution of fetuses and young, fetal and birth weights and weight gain were normal and similar for both groups. Three dead foetuses were found in each of 2 treated animals and in 1 control animal. Average litter size was lower in the treated group (4.8 young per litter) than in the control group (7.6 young per litter). Macroscopic examinations of the young failed to reveal any teratogenic or other abnormalities.

Skin Tolerance Studies

Daily application of FUCIDIN OINTMENT (sodium fusidate) to the ears of rabbits for a period of one month evolved neither general intolerance, local irritation to the eye, change in capillary permeability of the treated region, nor sensitization to the irritant effects of locally applied chloroform.

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