PRODUCT MONOGRAPH

FLAMAZINE*

(SILVER SULFADIAZINE CREAM) 1%

STERILE

TOPICAL ANTIBACTERIAL AGENT

3HN730026E

Smith & Nephew Inc.
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NAME OF THE DRUG

FLAMAZINE

(Silver Sulfadiazine cream) 1%

STERILE

CLASSIFICATION

TOPICAL ANTIBACTERIAL AGENT

ACTION

The mechanism of silver sulfadiazine's antibacterial action has not been fully elucidated. After exposure to the drug, structural changes in the bacterial cell membrane occur, including distortion and enlargement of the cell and a weakening of the cell wall membrane. This is accompanied by reduced viability in sensitive strains due to interference with macromolecular synthesis. The sulfadiazine moiety also provides a bacteriostatic action against sensitive organisms.

In adults, up to 10% of the sulfadiazine may be absorbed and 60-85 % of the absorbed amount is excreted in the urine. In children with 13 % body surface area burns, the urinary sulfadiazine concentration was 31.8 mg/L.

INDICATIONS AND CLINICAL USE

FLAMAZINE (silver sulfadiazine cream) is indicated for the treatment of leg ulcers, burns, skin grafts, incisions and other clean lesions, abrasions, minor cuts and wounds.

FLAMAZINE cream is especially indicated in the treatment and prophylaxis of infection in serious burn victims.

CONTRAINDICATIONS

Sulfonamide therapy is known to increase the possibility of kernicterus. FLAMAZINE cream should not be used in pregnant females at term, in premature infants, or in newborn infants during the first months of life.

FLAMAZINE cream should not be used on patients with a known sensitivity to any of its components.

WARNINGS

Sensitization to topically applied silver sulfadiazine is rarely predicted or proven by patch testing. Caution should be exercised in the use of FLAMAZINE cream in individuals who have previously shown sensitization reactions to sulfonamides.

Silver sulfadiazine cream should be used with caution on patients with a history of glucose - 6 - phosphate dehydrogenase deficiency as hemolysis may occur.

When treatment with silver sulfadiazine cream involves prolonged administration and/or large burned surfaces, considerable amount of silver sulfadiazine is absorbed. Serum concentration of sulfadiazine may approach adult therapeutic levels (8-12 mg %). Use of FLAMAZINE may delay separation of burn eschar and may alter the appearance of burn wounds.

PRECAUTIONS

FLAMAZINE (silver sulfadiazine cream) should be used with caution in patients with significant hepatic or renal impairment as both may reduce the elimination of absorbed sulfadiazine.

Leukopenia has been reported following the use of silver sulfadiazine, especially patients with large area burns. This may be a drug-related effect, and often occurs 2-3 days after treatment has commenced. It is usually self-limiting and therapy with FLAMAZINE cream does not normally need to be discontinued, as the WBC count usually returns to the normal range in a few days. WBC counts should be closely monitored.

Use in pregnancy

The safe use of FLAMAZINE has not been established in pregnancy. FLAMAZINE cream should only be used in badly burned pregnant women if the benefit to the patient outweighs the risk to the foetus. FLAMAZINE cream should not be used when the patient is near term. (SEE CONTRAINDICATIONS)

Use in breast feeding

The sulphonamide concentration of breast milk is 15-35% of that in the serum. Since all sulphonamides increase the possibility of kernicterus, caution is required in nursing mothers.

Drug interactions

Enzymatic debriding agents

FLAMAZINE may inactivate enzymatic debriding agents; thus the concomitant use of these compounds may be inappropriate.

Oral hypoglycemic agents and Phenytoin

In patients with large area burns where serum sulfadiazine levels may approach therapeutic levels, the action of oral hypoglycemic agents and Phenytoin may be potentiated and it is recommended that blood levels be monitored.

Cimetidine

In patients with large area burns, it has been reported that co-administration of cimetidine may increase the incidence of leukopenia.

ADVERSE REACTIONS

Renal & Urinary Disorders

Very rare:
- Renal failure

Blood & Lymphatic Tissue Disorders

Common:
- Leukopenia

  Leukopenia has been reported in up to 3-5% of patients treated with FLAMAZINE cream. This may be a drug-related effect, and often occurs within 48-72 hours after therapy has commenced. It is usually self-limiting and therapy with FLAMAZINE does not usually need to be discontinued, although the blood count must be carefully monitored to ensure that it returns to normal within a few days.

Skin & Subcutaneous Tissue Disorders

Common:
- Application site rash, including eczema and contact dermatitis, may occur in about 2% of patients.
- Pruritus

Rare:
- Argyria

  There is evidence that in large area burn wounds

and/or after prolonged application, systemic absorption of silver can occur causing clinical argyria.

General Disorders and/or Administration Site Conditions

Common: Application site burning, rash and itching.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In extensively burned patients or in patients suspected of showing symptoms of excessive absorption, it is important to optimally maintain fluid balance not only to prevent dehydration but also to avoid the possibility of renal impairment.

DOSAGE AND ADMINISTRATION

Burns

The burn wounds should be cleaned and FLAMAZINE cream applied over all the affected areas to a depth of 3 - 5 mm.

One technique is to apply the cream with a sterile gloved hand and/or sterile spatula. Where necessary, the cream should be re-applied to any area from which it has been removed by patient activity.
FLAMAZINE cream should be re-applied at least every 24 hours.

Hand burns and fingers injuries

One recommended method, which has been found successful, is to apply FLAMAZINE cream to the burn and the whole hand is then enclosed in a clear plastic bag or glove, which is then closed at the wrist. The patient should be encouraged to move the hand and fingers. The dressing should be changed every three days or when an excessive amount of exudate has accumulated in the bag.

Leg Ulcers

One acceptable method involves filling the cavity of the ulcer with FLAMAZINE cream to a depth of at least 3-5 mm. Care should be taken to prevent the spread of the cream onto non-ulcerated areas. The cream should be followed by an absorbent pad or gauze dressing, with further application of pressure bandaging as appropriate for the ulcer. The dressing should be changed every 2 or 3 days, with cleaning and debriding being performed before application of FLAMAZINE cream.

It is not recommended that FLAMAZINE cream be used in leg ulcers that are very exudative.

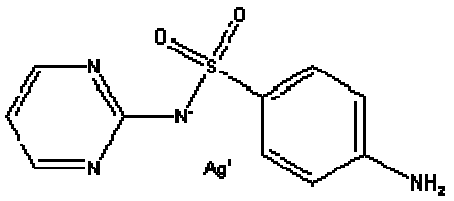
A container of FLAMAZINE cream should be reserved for use for a specific patient.

PHARMACEUTICAL INFORMATION

Trade Name: FLAMAZINE cream

U.S.A.N.: Silver Sulfadiazine

Structural Formula:



Chemical Name: Silver 2-(4-aminobenzenesulfonamido)-pyrimidine

Molecular Formula: $C_{10}H_9N_4O_2SAg$

Molecular Weight: 357.14

Description

Silver sulfadiazine is a light-stable white powder, very slightly soluble in water and most organic solvents, but readily soluble in nitric acid and concentrated ammonia solutions.

Composition

FLAMAZINE cream is a white cream containing 1% w/w silver sulfadiazine in a water soluble vehicle. The pH of the cream is between 3.5-6.0.

Inactive ingredients

Polysorbate 60 – vegetable grade
Polysorbate 80 – vegetable grade
Glyceryl Stearate
Cetyl Alcohol
Propylene Glycol
Liquid Paraffin
Distilled Water

Sterility

FLAMAZINE cream is a sterile compound and contains no preservatives.

Dosage Forms

FLAMAZINE cream is a white cream and is available in the following containers: 500 g jars, 20 g and 50 g tubes. FLAMAZINE cream should be stored at 8° to 25°C. To ensure sterility the 500 g jars should be discarded 24 hours after opening and tubes of FLAMAZINE 7 days after opening.

MICROBIOLOGY

The minimum inhibitory concentration (MIC) as determined by the serial tube dilution of susceptible organisms is shown in Tables 1 & 2.

TABLE #1

Minimum Inhibitory Concentration of Silver Sulphadiazine in mg/L

		At 24 hours		At 3 days	
ORGANISM	STRAINS	Expt.1	Expt.2	Expt.1	Expt.2
Pseudomonas aeruginosa	(SNR)	25	<6	100	100
Pseudomonas aeruginosa	6750 NCTC	25	12,5	100	12,5
Pseudomonas aeruginosa	USA 1*	>100	300	>100	>300
Pseudomonas aeruginosa	USA 4*	25	25	>100	>300
Pseudomonas aeruginosa	6741 NCTC	50	12,5	100	100
Pseudomonas aeruginosa	8203 NCTC	50	25	50	>100
Pseudomonas aeruginosa	661322 NCTC	50	37,5	>100	300
Aerobacter aerogenes	749 NCTC	25	>18,7	100	25
Escherichia coli	(SNR)	50	37,5	>100	150
Proteus vulgaris	(SNR)	25	37,5	>100	150
Staphylococcus aureus	(OxH)6571	50	50	100	100
Candida albicans	(SNT)	100	300	>100	>300
Aspergillus niger	(SNR)	25	18,7	>100	300

*These strains were isolated from burn patients treated with silver nitrate.

TABLE #2

The Susceptibility to Silver Sulphadiazine of 643 Isolates of 14 Bacterial Species.

Organism	No. Tested	Minimal Inhibitory Concentrations (cumulative percentage) mg/L Silver Sulphadiazine							
		<0,78	1,56	3,13	6,25	12,5	25	50	100
Pseudomonas aeruginosa	130	0,8	5,4	29,2	60,0	79,2	93,1	100	-
P.multiphilia	7	14,3	14,3	28,6	42,9	85,8	100	-	-
Klebsiella	54	7,4	11,1	14,8	31,5	61,1	74,1	98,2	100
Enterobacter (except E.cloacae)	50	0	8,0	10,0	20,0	44,0	66,0	96,0	100
E.cloacae	24	0	4,2	4,2	20,8	45,8	79,2	100	-
Escherichia coli	63	3,2	6,3	30,2	50,8	71,4	90.5	100	-
Proteus Mirabilis	53	24,5	50,9	73,6	88,7	96,2	96,2	100	-
P.morganii	10	10,0	30,0	40,0	80,0	80,0	90,0	100	-
Serratia	28	7,1	25,0	39,3	75,0	89,3	92,9	96,4	100
Citrobacter	10	20,0	20,0	40,0	60,0	60,0	80,0	100	-
Herellea	9	11,1	22,2	55,6	66,7	77,8	88,9	100	-
Staphylococcus aureus	101	3,0	6,0	16,9	27,8	37,7	76,3	99,1	100
S.epidermidis	51	3,9	7,8	29,4	51,0	74,5	86,3	100	-
Enteroccoccus(group D Streptococcus)	53	0	0	0	0	0	1,9	96,2	100

CLINICAL PHARMACOLOGY

Silver sulfadiazine is released slowly from the cream and thus, rapid depletion of chloride and associated electrolyte disturbances are minimized. Silver sulfadiazine is not inhibited by PABA.

In burned pigs, the absorption of silver was less than 1% of the applied dose, however 5 to 8% of the sulfadiazine was absorbed. There is very little penetration of the silver below the outer layers of the wound surface, and the largest amount of the absorbed silver is found in the liver. In addition, high concentrations of silver have been measured in the bile, which suggest a hepatobiliary excretion of the silver moiety. The sulfadiazine moiety is excreted via the kidneys.

After a 500 to 1000 g application of 1% silver sulfadiazine, (corresponding to 5-10 g of silver sulfadiazine), to burn patients, serum levels of sulfadiazine were 2-5 mg/L, and the urine levels were 60-1000 mg/L. The daily urinary excretion of sulfadiazine was 100-200 mg, corresponding to less than 5% of the applied amount of silver sulfadiazine.

The sulfadiazine concentration in burn wound exudate, was 900-1000 mg/L 24 hours after application, which is approximately 20 times the MIC of sensitive bacteria (50 mg/L).

In one study of 23 patients, mean silver serum levels were moderately higher than the normal range however the urinary excretion of silver, was markedly elevated (0.402 mg/24h). The six patients with 60% or greater B.S.A. burns had a mean peak excretion of 1.100 mg/24 hours (approximately 1,0000 times the normal level). None of the patients had silver toxicity.

TOXICOLOGY

Acute Toxicity

The following LD_{50}'s were determined in mice, rats, guinea pigs, and rabbits.

SPECIES	ROUTE	LD_{50}
Mice (male)	I.P.	37,8 mg/kg
Rats (both sexes)	S.C.	> 2,150 mg/kg
Guinea pigs (both sexes)	S.C.	> 2,150 mg/kg
Rabbits (both sexes)	S.C.	> 2,150 mg/kg
Newborn rats	Oral	482 mg/kg
Adult rats (both sexes)	Oral	> 10,000 mg/kg

Subacute Studies

Ointments containing 1, 8 and 20% silver sulfadiazine were applied to the abraded and occluded skin of rabbits for six hours each day, seven days a week for three consecutive weeks. Additional groups of rabbits were treated with the ointment without silver sulfadiazine or received no treatment, and therefore served as procedural controls.

The same ointments were also applied to the intact and non-occluded skin of rabbits for six hours a day, seven days a week for thirteen consecutive weeks. An additional group of rabbits was treated with the ointment without silver sulfadiazine.

The ointment base alone and the ointments containing silver sulfadiazine elicited mild irritation of the skin. The irritation produced by the silver sulfadiazine ointment was similar to or slightly less than the ointment alone.

Varying degrees of skin inflammation were observed histologically at week 13 in both ointment base and high concentration silver sulfadiazine ointment treated rabbits.

Urinary pH was lower at week 3 in the male rabbits treated with the high concentration of silver sulfadiazine and the ointment base alone.

There was a tendency to lowered RBC counts at 13 weeks in female rabbits treated with the high concentration of silver sulfadiazine.

Serum protein levels were elevated in some rabbits treated with the high concentration and with the ointment base alone.

In all other respects including food consumption, bodyweight change, ophthalmoscopy, urinalysis, blood chemistry, haematology, organ weights, macroscopic and microscopic pathology, the rabbits treated with silver sulfadiazine ointment remained comparable with the ointment base and "no treatment" control groups.

Skin Irritation Studies

The primary irritation potential of silver sulfadiazine cream was assessed using an occlusive patch test technique in rabbits. The primary irritation index was zero.

Eye Irritation Studies

Eye irritation studies in the rabbits revealed no behavioural indications of discomfort immediately after treatment. Four out of six animals had slightly red lids when observed after one hour, but this had completely disappeared by the time of the second observation at 24 hours. No other symptoms were observed.

Sensitivity Studies

The sensitizing potential of the silver sulfadiazine cream was assessed in guinea pigs using a standard technique. A positive control group was included in which the guinea pigs were challenged with the known sensitizer 2, 4-dinitrochlorobenzene. The animals were shown to be capable of sensitization by a positive response to the latter compound, but did not react by sensitization to the silver sulfadiazine cream.

Teratological Studies

A study was conducted in rabbits using a control (placebo cream), 3% or 10% cream. 5 mL cream was applied to their shaved backs for four (4) hours each day, from day 6 through day 18 of gestation. There were no compound-related effects upon reproductive or fetal parameters observed in either the 3% or 10% groups. Variations between the silver sulfadiazine treated groups and the control groups were within the normal range of intergroup variations in studies of this type and were not significant.

REFERENCES

1. Boosalis, M.G., McCall, J.T., Ahrenholz, D.H., Solem, L.D., McClain, C.J., Serum and urinary silver levels in thermal injury patients, Surgery 1987, Vol. 101, No. 1, pp. 40-43.

2. Caffee, H.H., Bingham, H.G., Leukopenia and silver sulfadiazine, The Journal of Trauma 1982, Vol. 22, No. 1, pp. 586-587.

3. Chan, C.K., Jarrett, F., Moylan, J.A., Acute leukopenia as an allergic reaction to silver sulfadiazine in burn patients, The Journal of Trauma 1976, Vol. 16, No. 5, pp. 395-396.

4. Charoonsmith, T., Satienchoke, M., Tittiranonda, T., Tiewtranonda, P., Silver sulfadiazine in the treatment of burns, The Journal of Medical Association Thailand 1976, Vol. 59, No. 7, pp. 301-304.

5. Conly, J.M., Byrne, S., McLeod, J., Hoban, S., Robertson, G., Ronald, A.R., Antimicrobial cream susceptibility testing, Burns 1985, Vol. 12, pp. 91-96.

6. De Boer, P., Collinson, P. O., The use of silver sulfadiazine occlusive dressings for finger-tip injuries, Journal of Bone, Joint Surgery 1981, Vol. 63B, No. 4, pp. 545-547.

7. Degreef, H., Michiels, J.L., 1% silver sulfadiazine cream as a treatment for infected leg ulcers, The Current Therapeutic Research Journal 1984, Vol. 36, No. 6, pp. 1190-1194.

8. Degreef H., Dooms-Gossens, A., Patch testing with silver sulfadiazine cream, Journal of Contact Dermatitis 1984, Vol. 12, pp. 33-37.

9. Delaveau, P., Friedrich-Noue, PH., Sulfadiazine chez les brûlés, Thérapie 1977, Vol. 32, pp. 563-572.

10. Dessai, M.H., Herndon, D.N., Eradication of Candida burn wound septicemia in massively burned patients, The Journal of Trauma 1988, Vol. 25, No. 2, pp. 140-145.

11. Dickinson, S.J., Topical therapy of burns in children with silver sulfadiazine, New York State Journal of Medicine 1973, pp. 2045-2048.

12. Fox, C.L. jr., Silver sulfadiazine - A new topical therapy for Pseudomonas in burns, Journal of Arch. Surgery 1968, Vol. 96, pp. 185-188.

13. Fox, C.L. jr., Rappole, B.W., Stanford, W., Control of Pseudomonas infection in burns by silver sulfadiazine, Journal of Surgery, Gynecology and Obstetrics 1969, pp. 1021-1026.

14. Fox, C.L. jr., Silver sulfadiazine for control of burn wound infections, The International Journal of Surgery 1975, Vol. 60, No. 5, pp. 275-277.

15. Fox, C.L. jr., Topical therapy and the development of silver sulfadiazine, Surgery, Gynecology and Obstetrics Journal 1983, Vol. 157, pp. 82-88.

16. Fox, C.L., Modak, S.M., Stanford, W., Silver treated graft materials for coverage of infected burn wounds, Journal of Plastic Surgery 1979, Vol. 24, No. 3, pp. 265-267.

17. Hoffmaan, S., Medicines information: Silver sulfadiazine, Vgeskr-Laeger 1984, Vol. 146, No. 30, pp. 2250-2252.

18. Hoffmaan, S., Silver sulfadiazine: An antibacterial agent for topical use in burns, The Scandinavian Journal of Plastic Reconstruction Surgery 1984, Vol. 18, pp. 119-126.

19. Jarret, F., Ellerbe, S., Demiing, R., Acute leukopenia during topical burn therapy with silver sulfadiazine, Department of Surgery, Un iversity of Wisconsin 1978, Vol. 135.

20. Kiker, R.G., Carvajal, H.F., Mlcak, R.P., Larson, D.L., A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children, The Journal of Trauma 1977, Vol. 17, No. 11, pp. 835-836.

21. Lazare, R., Watson, P.A., Winter, G.D., Distribution and excretion of silver sulfadiazine applied to scalds in the pig, Burns, Vol. 1, No. 1, pp. 57-84.

22. Lockhart, S.P., Rushworth, A., Azmy, A.A.F., Raine, P.A.M., Topical silver sulfadiazine: Side effects and urinary excretion, Burns 1982, Vol. 10, pp. 9-12.

23. MacMillan, B.G., The control of burn wound sepsis, Intensive Care Medicine 1981, Vol. 7, pp. 63-69.

24. McDougall, I.A., Burns and the use of silver sulphadiazine, Australian, New Zealand Journal of Surgeons 1972, Vol. 42, No. 2, pp. 174-178 .

25. McManus, A.T., Denton, C.L., Mason, A.D. jr., Mechanisms of in vitro sensitivity to sulfadiazine silver, The Journal of Arch. Surgery 1983, Vol. 118, pp. 161-168.

26. Rosenkranz, H.S., Rosenkranz, S., Silver sulfadiazine: Interaction with isolated deoxyribonucleic acid, Journal of Antimicrobial Agents and Chemotherapy 1972, Vol. 2, No. 5, pp. 373-383.

27. Rosenkranz, H.S., Carr, H.S., The determination of susceptibility of bacterial isolates to silver sulfadiazine, Journal of Chemotherapy 1978, Vol. 24, pp. 143-145.

28. Sano, S., Fujimori, R., Takashima, M., Itokawa, Y., Absorption, excretion and tissue distribution of silver sulfadiazine, Burns 1981, Vol. 8, pp. 278-285.

29. Snelling, C.F.T., Ronald, A.R., Waters, R., Yamorski, D.S., Drulak, K., Sunderland, M., Comparison of silver sulfadiazine and gentamicin for topical prophylaxis against burn wound sepsis, CMA Journal 1978, Vol. 119, pp. 466-470.

30. Stanford, W., Rappole, B.W., Fox., C.L., Clinical experience with silver sulfadiazine, a new topical agent for control of pseudomonas infections in burns, The Journal of Trauma 1969, Vol. 9, No. 8, pp. 377-388.

31. Wysor, M.S., Zollinhofer, R.E., On the mode of action of silver sulfadiazine, Journal of Pathology and Microbiology 1972, Vol. 38, pp. 296-308.

32. Coward, J.E. & Rosenkranz, H.S., Electron Microscopic Appearance of Silver Sulfadiazine-Treated Enterobacter cloacae, Chemotherapy 21, 231 1975.

33. Coward, J.E. Carr, H.S. & Rosenkranz, H.S., Silver sulfadiazine: Effect on growth and ultrastructure of Staphylococci. Chemotherapy 19, 348 1973b.

34. Akahane, T. & Tsukada, S., Electron-microscopic observation on silver deposition in burn wounds treated with silver sulfadiazine cream. Burns 8, 271 1982.

35. Roe, E.A. & Jones, R.J., Leucocyte responses of burned mice given mixed Gram-negative infections and treated topically with creams containing silver compounds. Burns 3, 72 1977.

36. Skornik, W.A. & Dressler, D.P., Topical antisepsis studies in the burned rat. Arch. Surg. 103, 469 Oct. 1971.

37. Lloyd, J.R., Improved management of skin graft donor sites with silver sulfadiazine dressings. Arch. Surg. 108, 561 1974.

38. Carr, H.S., Wlodkowski, T.J., & Rosenkranz, H.S., Silver sulfadiazine: In vitro antibacterial activity. Antimicrob Ag. Chemother 4, 585 1973.

39. Babb, J.R., Bridges, K., Jackson, D.M., Lowbury, E.J.L., & Ricketts, C.R., Topical Chemoprophylaxis: trials on silver phosphate chlorhexidine, silver sulfadiazine and povidone iodine preparations. Burns 3,2, 65 Jan. 1977.

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