PRODUCT MONOGRAPH

FLAMAZINE*

(SILVER SULFADIAZINE CREAM) 1%

STERILE

TOPICAL ANTIBACTERIAL AGENT

DIN #00323093

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Smith & Nephew Inc.
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Control No. 211660

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. To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLAMAZINE and other antibacterial drugs, FLAMAZINE should be used only to treat infections that are proven or strongly suspected to be cause by susceptible bacteria.

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.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing FLAMAZINE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks development of resistant organisms.

Potential for Microbial Overgrowth

The use of FLAMAZINE may promote the selection on non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

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.

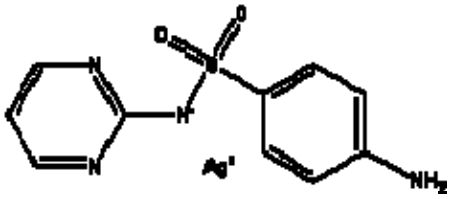
A container of FLAMAZINE cream should be reserved for use for a specific patient.

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 8º to 25ºC. 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.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLAMAZINE
Silver Sulfadiazine Cream 1%

Read this carefully before you start taking **FLAMAZINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLAMAZINE**.

What is FLAMAZINE used for?

Treatment of infections caused by bacteria which can be killed by FLAMAZINE:

- Infection in serious burn victims.
- Infection in leg ulcers, burns, skin grafts, incisions and other clean lesions, abrasions, minor cuts and wounds.

Antibacterial drugs like FLAMAZINE treat only bacterial infections. They do not treat viral infections.

How does FLAMAZINE work?
This medicine kills bacteria or stops their growth. This helps reduce or prevent infections. The time taken for the medicine to work will vary by wound type.

What are the ingredients in FLAMAZINE?
Medicinal ingredients:

- Silver sulfadiazine

Non-medicinal ingredients:

- Cetyl alcohol
- Distilled water
- Glyceryl stearate
- Liquid paraffin
- Polysorbate 60 – vegetable grade
- Polysorbate 80 – vegetable grade
- Propylene glycol

FLAMAZINE comes in the following dosage forms:

- FLAMAZINE Cream 1% is supplied in 500g jars and 20g or 50g tubes

Do not use FLAMAZINE if:

- it is during the last month of your pregnancy.
- it is during the first few months after birth for newborn or premature infants.
- you are allergic to silver sulfadiazine, cetyl alcohol, propylene glycol or any of the other ingredients of FLAMAZINE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLAMAZINE. Talk about any health conditions or problems you may have, including if you:

- have previously had allergic reactions to sulfonamides.
- have a glucose-6-phosphate dehydrogenase (G6PD) deficiency. Using sulfonamides like FLAMAZINE can lead to hemolysis (red blood cell breakdown).
- have liver or kidney problems. have previously had low white blood cell levels. Leukopenia (lowered white blood cell levels) has occurred after use of FLAMAZINE. Your doctor may order tests to monitor your white blood cell count while you are taking FLAMAZINE.
- are pregnant or are planning to become pregnant. FLAMAZINE may cause harm to unborn children. Only use this medicine if your doctor thinks the benefit is greater than the risk to the unborn child. Do not use this medicine if you are in the last month of your pregnancy.
- are breast feeding or intend to breast feed. FLAMAZINE can pass into breast milk and cause harm to your baby. Talk to your doctor about how to feed your baby when you are on FLAMAZINE.

Other warnings you should know about:

- Do not use this medicine for longer than advised by your doctor. This may lead to increased chance of side effects.
- If you are using FLAMAZINE to treat large wounds, it is important to drink lots of liquids prevent dehydration and kidney damage.
- FLAMAZINE may increase the time for dead tissue(eschar) to separate from the body. It may also change the appearance of burn wounds.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLAMAZINE:

- Enzymatic debriding agents (remove dead tissue from wounds).
- Oral hypoglycemic agents (for treatment of type 2 diabetes)
- Phenytoin (prevents seizures).
- Cimetidine (used for heartburn and ulcers).

Your healthcare professional may need to run blood tests if you are taking any of these medicines while taking FLAMAZINE.

How to take FLAMAZINE

- For topical (body surface) useonly.
- Although you may feel better in early treatment, FLAMAZINE should be used exactly as directed.
- Misuse or overuse of FLAMAZINE could lead to growth of bacteria that will not be killed by FLAMAZINE (resistance). This means that FLAMAZINE may not work for you in the future.
- Do not share your medicine. Each jar or tube of FLAMAZINE should be used on one person only.

Usual dose:

Burns:

- Clean the wound.
- Apply a 3mm – 5mm layer of the cream to the burned area using a sterile (germ-free) glove and/or sterile spatula.
- Reapply cream if it comes off or rubs away..
- Reapply cream at least every 24 hours or more frequently if wound fluid levels are high

Hand burns and finger injuries:

- Clean the wound.
- Apply a 3mm – 5mm layer of the cream to the affected area using a sterile (germ-free) glove and/or sterile spatula.
- Place whole hand in a clear plastic bag or glove and close at the wrist.
- Move your hands and fingers as regularly as possible
- Change the dressing every 3 days or more regularly if wound fluid levels are high.

Leg ulcers:

- Fill ulcer wound with cream to a depth of at least 3mm – 5mm.
- Apply cream to wound area only and avoid non-ulcerated areas.
- Apply an absorbent pad or gauze dressing.
- Apply pressure bandaging over the pad/dressing as advised by your doctor
- Change the dressing every 2 or 3 days.
- Cleaning and removal of dead tissue should be performed before each reapplication of FLAMAZINE.

Do not apply FLAMAZINE to leg ulcers which have large amounts of wound fluid.

Overdose:

An overdose of topically applied silver sulfadiazine is unlikely to cause life-threatening symptoms although the exact effects are unknown. Overdose of sulfadiazine by mouth may lead to diarrhoea or a feeling of sickness.

If you think you have taken too much FLAMAZINE contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use FLAMAZINE, apply it as soon as you remember. If it is close to the time when you are due to apply your next dose, wait and apply your next scheduled dose and then continue as before. Do not apply extra FLAMAZINE to make up for missed doses.

What are possible side effects from using FLAMAZINE?
These are not all the possible side effects you may feel when taking FLAMAZINE. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects:

- Leukopenia (lowered white blood cells) has been reported in burns patients treated with FLAMAZINE. Your doctor may order blood tests to monitor your white blood cell level while you are taking FLAMAZINE.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Application site rash (including eczema and contact dermatitis**) with symptoms of: • abnormal changes in skin colour and texture – red rashes, • itchy skin (which can be dry, cracked and scaly), • bumps, blisters, swelling, burning and tenderness.		✓	
RARE **Argyria** (skin discolouration): blue-grey discolouration of the skin		✓	
VERY RARE			✓

Renal failure (kidney failure) with symptoms of: • oliguria (passing small amounts of urine), • anuria (passing no urine), discoloured dark urine, • oedema (puffiness) of the feet/legs, • swelling of the abdomen, • weight gain, • fatigue (tiredness), • lethargy (lack of energy), • nausea, • vomiting and generally feeling unwell. • seizures (fits) or • coma.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 8ºC and 25ºC and protect from light.

Dispose of FLAMAZINE 500g jars 24 hours after opening.

Dispose of FLAMAZINE 20g or 50g tubes 7 days after opening.

Keep out of reach and sight of children.

If you want more information about FLAMAZINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (http://www.smith-nephew.com/canada) or by calling 1-800-463-7439.

This leaflet was prepared by Smith & Nephew Inc.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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