

PRODUCT INFORMATION

Name of the Medicine:

FLAMAZINE[®] CREAM 1.0% w/w

Silver sulfadiazine 1% w/w

Composition: *Active ingredient.* Silver sulfadiazine. *Excipients.* Polysorbate 60 Ph. Eur, Polysorbate 80 Ph. Eur, Glyceryl Monostearate Ph. Eur, Cetyl Alcohol Ph. Eur, Liquid Paraffin Ph. Eur, Propylene Glycol Ph. Eur and Purified Water Ph. Eur.

Description:

A sterile white hydrophilic cream containing silver sulfadiazine 1%. The cream is a semisolid oil-in-water emulsion. The silver sulfadiazine is in a fine micronised form.

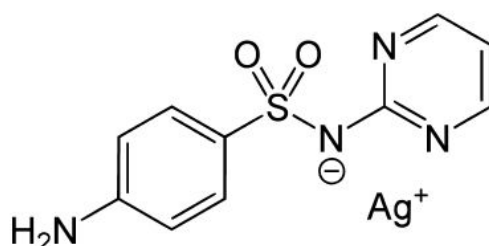
Silver sulfadiazine is a white or creamy-white, odourless or almost odourless crystalline powder, which becomes yellow on exposure to light. Practically insoluble in water; slightly soluble in acetone; practically insoluble in alcohol, chloroform or ether; freely soluble in strong ammonia solution.

Chemical name:

Silver salt of N'-(pyrimidin-2-yl)sulphanilamide. C₁₀H₉AgN₄O₂S. M.W. 357.1

CAS 22199-08-2

Chemical structure:



Pharmacology:

Silver sulfadiazine is a sulfonamide and has broad antimicrobial activity against both Gram-positive and Gram-negative organisms.

Silver sulfadiazine acts on the cell membrane and cell wall. Unlike sulfadiazine or other sulfonamides, the antibacterial action of the silver salt of sulfadiazine does not appear to depend on inhibition of folic acid synthesis. Its action is not antagonised by p-aminobenzoic acid.

Microbiology:

Silver sulfadiazine has broad antimicrobial activity against both Gram-positive and Gram-negative organisms including *Pseudomonas aeruginosa*, some yeasts and fungi. It has also been reported to be active *in vitro* against herpes virus and *Treponema pallidum*.

Sulfonamides act by interfering with the synthesis of nucleic acids in sensitive micro-organisms by blocking the conversion of *p*-aminobenzoic acid to the co-enzyme dihydrofolic acid. Silver sulfadiazine has a bactericidal action; in contrast to sulfadiazine, the silver salt acts primarily on the cell membrane and cell wall and its action is not antagonised by *p*-aminobenzoic acid. Resistance to silver sulfadiazine has been reported and may develop during therapy.

Pharmacokinetics:

Silver sulfadiazine is slowly metabolised in contact with wound exudates. Up to about 10% of the sulfadiazine may be absorbed; concentrations in blood of 10 to 20 micrograms / millilitre have been reported although higher concentrations may be achieved when extensive areas of the body are treated. Some silver may be absorbed.

There is evidence that in large area wounds and/or after prolonged application, systemic absorption of silver can occur causing clinical argyria. The sulfadiazine readily diffuses across wounds and enters the general circulation. The degree of uptake will significantly depend upon the nature of the wound and the dosing regime. Sulfadiazine is excreted in the urine.

Indications:

FLAMAZINE cream is indicated for the prevention and treatment of infection in burns. Other types of wounds, such as pressure sores and leg ulcers, may also benefit from the application of FLAMAZINE cream.

Contraindications:

As sulfonamides are known to cause kernicterus, FLAMAZINE cream should not be used at, or near term pregnancy, on premature infants or on newborn infants during the first months of life. FLAMAZINE cream is also contraindicated in patients known to be hypersensitive to silver sulfadiazine or to other components of the preparation such as cetyl alcohol or propylene glycol.

Precautions:

- Transient leucopenia has occurred although its association with application of FLAMAZINE has not been confirmed. Nevertheless, regular blood counts are advisable in patients on long-term treatment.
- Patients should be watched carefully for sensitivity, especially if there are known reactions to sulfonamides.

- FLAMAZINE should be used with caution in patients with impaired renal or hepatic function. Sensitivity has been shown to occur but the incidence is lower than with other sulfonamides.
- Local reactions have been reported in patients treated with silver sulfadiazine; the separation of the eschar may be delayed and fungal invasion of the wound may occur.
- In patients with extensive burns, serum sulfonamide concentrations and renal function should be monitored and urine examined for sulfonamide crystals. Absorption of propylene glycol contained in the cream can affect serum osmolality which can interfere with some laboratory tests.
- The use of FLAMAZINE cream in some cases of glucose-6-phosphate dehydrogenase-deficient patients may be hazardous as haemolysis may occur.
- During treatment of burns over a large body area, significant amounts of silver sulfadiazine are systemically absorbed. Therefore, it is possible that any adverse reactions associated with sulfonamides may occur.

Effects on Fertility

No data were available from studies in animals following topical administration of silver sulfadiazine. No treatment-related effects on male or female fertility were documented following subcutaneous administration of silver sulfadiazine to rats at doses up to 500mg/kg/day for two (females) or ten (males) weeks prior to mating.

Use in Pregnancy (Category C)

Sulfonamides may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfonamides should therefore be avoided as far as possible during the last month of pregnancy. Fetal findings (abdominal hernia and laevorotation of the heart) occurred in low incidence in rats at subcutaneous doses of ≥ 250 mg/kg/day during early embryonic development and organogenesis. The significance of these findings for clinical topical administration is unknown.

Use in Lactation

FLAMAZINE should be used with caution in breast-feeding mothers. Systemically, sulfadiazine can be excreted in breast milk although at concentrations 15 -35% of those found in serum.

Paediatric Use

FLAMAZINE should not be used on premature infants or on newborn infants in the first few months of life (see Use in Pregnancy and Contraindications)

Use in the Elderly

Of the total number of subjects in clinical studies of Silver sulfadiazine cream, seven percent were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Carcinogenicity

Long-term carcinogenicity studies of silver sulfadiazine have not been conducted. Silver sulfadiazine is well established in clinical practice in several countries over a number of decades without any grounds for suspicion of carcinogenic potential in humans.

Genotoxicity

Silver sulfadiazine was not genotoxic in an *in vitro* bacterial reverse mutation assay or an *in vivo* mouse micronucleus test (PO administration), although the doses administered were considered low.

Interactions with other Medicines:

As silver may inactivate enzymatic debriding agents, their concomitant use may be inappropriate.

In large-area burns where serum sulfadiazine levels may approach therapeutic levels, it should be noted that the effects of systemically administered drugs may be altered. This can especially apply to oral hypoglycaemic agents and to phenytoin. In the case of these drugs, it is recommended that blood levels should be monitored as their effects can be potentiated.

Cimetidine: in patients with large area burns, it has been reported that coadministration of cimetidine may increase the incidence of leukopenia.

Sulfonamide may alter the effect of oral anticoagulants, methotrexate, and cyclosporine. There are isolated reports that sulfonamide may also interfere with the effectiveness of hormonal contraceptive.

Effect on Laboratory Tests:

In the treatment of burn wounds involving extensive areas of the body, the serum sulfonamide derivative concentrations may approach adult therapeutic levels (8 mg% to 12 mg%). Therefore, in these patients it would be advisable to monitor serum sulfonamide concentrations. Renal function should be carefully monitored and the urine should be checked for sulfonamide crystals. Absorption of the propylene glycol vehicle has been reported to affect serum osmolality, which may affect the interpretation of laboratory tests.

Adverse Effects:

- Blood & Lymphatic Tissue Disorders

Common: Leukopenia

Leukopenia has been reported in 3-5% of burns patients treated with FLAMAZINE. This may be a drug related effect, and often manifests itself 2-3 days after treatment has commenced. It is usually self-limiting and therapy with FLAMAZINE cream does not usually need to be discontinued, although the blood count must be monitored to ensure that it returns to normal within a few days.

- General Disorders & Administration Site Conditions

Common: Application site burning

- Renal & Urinary Disorders

Very rare: Renal failure

- Skin & Subcutaneous Tissue Disorders

Common: Pruritis

Common: Application site rash (including eczema and contact dermatitis)

Rare: Argyria

There is evidence that in large area wounds and/or after prolonged application, systemic absorption of silver can occur causing clinical argyria.

Dosage and Administration:

Method of administration:

To be applied topically.

Burns:

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

This application is best achieved 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.

In burns, FLAMAZINE cream should be re-applied at least every 24 hours, or more frequently if the volume of exudate is large.

Hand burns:

FLAMAZINE cream can be applied to the burn and the whole hand 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 when an excessive amount of exudate has accumulated in the bag.

Leg Ulcers/Pressure Sores:

The cavity of the ulcer should be filled with FLAMAZINE cream to a depth of at least 3-5mm. As FLAMAZINE cream can cause maceration of normal skin on prolonged contact, care should be taken to prevent spread onto non-ulcerated areas.

Application of FLAMAZINE cream should be followed by an absorbent pad or gauze dressing, with further application of pressure bandaging as appropriate for the ulcer.

The dressings should normally be changed daily but for wounds which are less exudative, less frequent changes (every 48 hours) may be acceptable. Cleansing and debriding should be performed before application of FLAMAZINE cream.

FLAMAZINE cream is not recommended for use in leg or pressure ulcers that are very exudative.

Overdosage:

Not likely to occur with normal usage.

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 failure.

If renal function is normal, fluids should be administered to maintain high urine output and assist in the rapid elimination of the drug.

For assistance contact the National Poisons Centre on 0800 POISON (0800 764 766).

Presentation:

Cream:

50g pre-printed cylindrical polyethylene tubes fitted with polyethylene caps.

500g black polypropylene jar fitted with a black polyethylene or polypropylene lid.

All tubes and jars are tamper-evident.

Storage Conditions:

FLAMAZINE should be stored below 25°C. Protect from light. The contents of one container are for the treatment of one person. 500g jars should be discarded 24 hours after opening. Tubes of FLAMAZINE should be discarded 7 days after opening.

Medicine Classification:

50g tube: Pharmacy Only Medicine

500g jar: Prescription Medicine

Name and Address of Sponsor:

Smith & Nephew Limited
621 Rosebank Road
Avondale
Auckland
New Zealand

◊ Trademark of Smith & Nephew