NEW ZEALAND DATA SHEET

1. PRODUCT NAME

FLAMAZINE CREAM 1.0% w/w

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains Silver sulfadiazine 1% w/w.
Excipients: Contains 4% cetyl alchol and 7% w/w propylene glycol.

For the full list excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream. White to off-white, oil in water, sterile homogeneous cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

To be applied topically.

Burns and Leg Ulcers/Pressure Sores: A layer approximately 3 to 5mm thick should be applied to the affected area using a sterile glove or spatula. The area should then be covered by an absorbent gauze dressing and support bandage where necessary. The dressing should be changed and FLAMAZINE cream applied at least every 24 hours in burn treatment, or at least three times weekly otherwise, and debridement carried out as necessary.
As Flamazine cream can cause maceration of normal skin on prolonged contact; care should be taken to avoid spread onto non-ulcerated areas.

4.3 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 any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

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.

Use in hepatic/renal impairment

FLAMAZINE should be use 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.

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.

Effects 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.

4.5 Interaction with other medicines and other forms of interaction

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 co-administration 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.

4.6 Fertility, pregnancy and lactation

Use in pregnancy – 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.

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.

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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed.

4.8 Undesirable 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

5.2 Pharmacokinetic properties

Absorption
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.

Elimination
Sulfadiazine is excreted in the urine.

5.3 Preclinical safety data

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

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.

Reproductive toxicology
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.

Fetal findings (abdominal hernia and laevorotation of the heart) occurred in low incidence in rats at subcutaneous doses of ≥250mg/kg/day during early embryonic development and organogenesis. The significance of these findings for clinical topical administration is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 60
Polysorbate 80
Glycerol Monostearate
Cetyl Alcohol
Liquid Paraffin
Propylene Glycol
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months from the date of manufacture.

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

20g*, 50g or 80g* pre-printed cylindrical polyethylene tubes fitted with polypropylene caps.

250g* or 500g black polypropylene jar fitted with a black polyethylene or polypropylene lid.

All tubes and jars are tamper-evident. * Pack sizes not marketed

6.6 Special precautions for disposal and other handling

The contents of one container are for the treatment of one person.

7. MEDICINE SCHEDULE

Flamazine Cream 1% w/w:
50g tube (Pharmacy Only Medicine)
500g jar (Prescription Medicine)

8. SPONSOR

Smith & Nephew Ltd
Unit A, 36 Hillside Road
Wairau Valley
Auckland 0627
New Zealand

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 29 October 2009

10. DATE OF REVISION OF THE TEXT

28 June 2019

Summary table of changes

Section Changed	Summary of new information

All	Reformat datasheet to comply with SmPC format
7	Change to Sponsor address