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Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Brand Name : **AGOBURN** **Generic Name** : Silver Sulfadiazine Cream USP 1% w/w		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing Information (Summary of Products Characteristics)

1. NAME OF DRUG PRODUCT

1. Name of drug product

Silver Sulfadiazine Cream USP 1% w/w

1.1 (Trade) name of product

AGOBURN

1.2 Strength

Each tube contains:
Silver Sulfadiazine USP 1% w/w

1.3 Pharmaceutical Dosage Form

Topical Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration

Each tube contains:
Silver Sulfadiazine USP 1% w/w

2.2 Quantitative Declaration

Ingredients	Specification	Label Claim	Qty. / Gram
ACTIVE			
Silver Sulfadiazine	USP 42	1% w/w	153.00 mg
NON ACTIVE			
Chlorocresol	BP 2019	-	15.00 mg
White soft paraffin	BP 2019	-	750.00 mg
Light liquid paraffin	BP 2019	-	750.00 mg
Cetomacrogol-1000	BP 2019	-	300.00 mg
Mono basic sodium phosphate	BP 2019	-	15.00 mg
Propyl paraben	BP 2019	-	5.100 mg
Methyl paraben	BP 2019	-	15.00 mg
Cetostearyl alcohol	BP 2019	-	1.200 g
Purified water	BP 2019	-	q.s.

USP 42 = United States Pharmacopoeia 42.
BP 2019 = British Pharmacopoeia 2019.

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3. PHARMACEUTICAL DOSAGE FORM

Topical Cream

White, homogenous, smooth cream free from grittiness.

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4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

AGOBURN cream 1% is a topical antimicrobial drug indicated as an adjunct for the prevention and treatment of wound sepsis in patients with second – and third – degree burns.

Prompt institution of appropriate regimens for care of the burned patient is of prime importance and includes the control of shock and pain. The burn wounds are then cleansed and debrided, and **AGOBURN** cream 1% is applied under sterile conditions. The burn areas should be covered with **AGOBURN** cream 1% at all times. The cream should be applied once to twice daily to a thickness of approximately 1/16 inch. Whenever necessary, the cream should be reapplied to any areas from which it has been removed by patient activity. Administration may be accomplished in minimal time because dressings are not required. However if individual patient requirements make dressings necessary, they may be used.

Reapply immediately after hydrotherapy.

4.2 Posology and Method of Administration

An application of **AGOBURN** cream 1% is the gentle massaging of several thin layers of cream into and around the sore of painful area. The number of thin layers controls the intensity of action. One thin layer provides mild effects two thin layers provide a strong effect and three thin layers provide a very strong effect.

Dosing interval : Apply 2 to 3 times daily.

Method of administration : Topical

4.3 Contraindications

AGOBURN Cream 1% is contraindicated in patients who are hypersensitive to Silver Sulfadiazine or any of the other ingredients in the preparation.

Because sulfonamide therapy is known to increase the possibility of kernicterus, **AGOBURN** Cream 1% should not be used on pregnant women approaching or at term, on premature infants, or on newborn infants during the first 2 months of life.

4.4 Special Warnings and Precautions for Use

If hepatic and renal functions become impaired and elimination of drug decrease, accumulation may occur and discontinuation of **AGOBURN** Cream 1% (Silver Sulfadiazine) should be weighed against the therapeutic benefit being achieved.

In considering the use of topical proteolytic enzymes in conjunction with **AGOBURN** Cream 1% the possibility should be noted that silver may inactivate such enzymes.

There is potential cross – sensitivity between Silver Sulfadiazine and other sulfonamides. If allergic reactions attributable to treatment with Silver Sulfadiazine occur, continuation of therapy must be weighed against the potential hazards of the particular allergic reaction.

Fungal proliferation in and below the eschar may occur. However, the incidence of clinically reported fungal super infection is low.

The use of **AGOBURN** Cream 1% (Silver Sulfadiazine) in some cases of glucose – 6-phosphate dehydrogenase – deficient individuals may be hazardous, as hemolysis may occur.

4.5 Interaction with Other Drugs, Other Forms of Interactions

Potentially hazardous interactions

Absorbed sulfadiazine is a competitive inhibitor of enzymes in the hepatic metabolism of phenytoins and tolbutamide.

Other significant interactions

In vitro studies have provided discrepant results as to whether topically applied cerium nitrate exerts synergism or antibacterial action of silver sulfadiazine. Certain animal experiments and clinical trials in burned patients failed to document a superiority of cerium nitrate/silver sulfadiazine cream over silver sulfadiazine cream alone. However, a significantly better protection against bacterial colonization of burn wounds was achieved with a cream nitrate, compared with 0.05% chlorhexidine baths, and the resulting dry firm burn eschar remained intact for several weeks, therapy providing a satisfactory wound cover until tangential excision eventually could be carried out.

The addition of Trimethoprim to silver sulfadiazine cream has been shown not to increase the prophylactic of the latter.

Potentially useful interactions

The clinical efficacy of silver sulfadiazine cream against colonization, especially with Staphylococus aureus, can be increased by the incorporation of chlorhexidine digluconate 0.2%.

A synergistic action of silver sulfadiazine and topical sodium piperacillin has been demonstrated in vitro and in animal experiments, but has so far not been evaluated in clinical trials.

4.6 Use in Pregnancy and Lactation

High maternal serum levels of absorbed sulfadiazine during the last week of pregnancy may cause kernicterus in the newborn infant. In case of large burn injuries in a pregnant woman, the threat imposed on the fetus by the burn itself, even if uninfected, and especially if infected, outweighs the risk of inducing kernicterus.

4.7 Effects on ability to drive and operate machine

No effect on the above. No sedation / drowsiness has been reported.

4.8 Undesirable effects

Infrequently occurring events include skin necrosis, erythema multiforme, skin discoloration, burning sensation, rashes, and intestitial nephritis.

Reduction in bacterial growth after application of topical antibacterial agents has been reported to permit spontaneous healing of deep partial-thickness burns by preventing conversion of the partial thickness to full thickness by sepsis. However, reduction in bacterial colonization has caused delayed separation, in some cases necessitating escharotomy in order to prevent contracture.

Absorption of Silver Sulfadiazine varies depending upon the percent of body surface area and the extent of the tissue damage. Although few have been reported it is possible that any adverse reaction associated with sulfonamides may occur. Some of the reactions, which have been associated with sulfonamides, are as follows: blood dyscrasias, including agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia and hemolytic anemia; dermatologic and allergic reactions, including Stevens-

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Johnson syndrome and exfoliative dermatitis; gastrointestinal reactions; hepatitis and hepatocellular necrosis; CNS reactions; and toxic nephrosis.

4.9 Overdoses

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.

If irritation develops, use of cream should be discontinued and appropriate therapy instituted.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco-Kinetic Properties

Up to 10% of the topically applied amount of sulfadiazine is absorbed. The absorption is higher from deep partial thickness burn wounds than from full thickness burn wounds, due to the avascularity of the letter. Reported serum sulfadiazine levels during therapy are generally in the range of 10-50 $mg.1^{-1}$, although levels of 100-150 $mg1^{-1}$occasionally may occur. The concentration of absorbed sulfadiazine can be measured in serum or urine by the Bratton and Marshall method. The specific determination of the parent sulfadiazine as well as its metabolites requires the use of high performance liquid chromatography. The limit of detection of sulfadiazine in plasma using this method is 400 $\mu g.1^{-1}$. For the determination of antimicrobial sulfonamide activity in body fluids, biological assays using suitable bacterial test strains will suffice. The concentration of silver in body fluids can be assayed by atomic absorption spectrophotometry.

After a single application of silver sulfadiazine cream to scalds in pigs, less than 1% of the silver is absorbed during the following 48 hours. In humans who had silver sulfadiazine cream applied daily to partial and full thickness burns covering a mean of 47% of the total body surface area, the overall mean serum silver concentration was approximately 300 $\mu g.1^{-1}$ and was twice as high in patients with > 60% burns (upper limit of normal range 200 $\mu g.1^{-1}$). The mean daily urinary excretion of silver was approximately 100-400 µg (normal range < 1 µg), sometimes exceeding 1000 µg in patients with > 60% burns.

Absorbed silver has been reported as the cause of serious toxic manifestations. No silver deposits were demonstrable by light microscopy or electron microscopy of renal tissue specimens obtained at necropsy of two patients who died from 80% and 90% partial and full thickness burns who had been treated with extensive amounts of silver sulfadiazine cream (up to 12 kg daily) for three weeks. Silver deposits have been demonstrated in the cytoplasm of epidermal cells and sweat glands in a patients who had silver sulfadiazine cream applied for 21 days to a 12% mixed superficial and deep dermal burn. Reversible silver deposits in the buccal mucosa were diagnosed in 2% of the patients in a burns center, where silver sulfadiazine was applied as an extraordinary highly concentrated suspension (20 or 50 %).

Absorbed sulfadiazine is excreted in the urine, peak concentrations ranging from 150 to 350 $mg.1^{-1}$.

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Oral absorption	
Sulfadiazine	≤10%
Silver	<1%
Presystemic metabolism	
Plasma half-life	
Range (sulfadiazine)	10-12 h
Mean	-
Volume of distribution (sulfadiazine)	0.36 $l.kg^{-1}$
Plasma protein binding (sulfadiazine)	29-45%

Sulfadiazine is excreted in breast milk, at concentrations 15-35% of those in serum. Absorbed sulfadiazine may also cross the placenta. Both renal and hepatic disease may reduce the elimination of absorbed sulfadiazine

Concentration-effect relationship

There are no published studies of a possible association between the in situ concentration of the two moieties during treatment of burns with silver sulfadiazine cream and the effect on the number of colonizing or infecting bacteria.

Metabolism

Absorbed sulfadiazine is metabolized in the liver by N_4-acetylation and by 5-hydroxylation. About 50% of the absorbed material is excreted as unchanged drug, with up to 40% as the acetylated metabolite. Absorbed silver , if any may remain in the body, predominantly in the liver, for long periods of time, being slowly excreted via the bile.

5.2 Pharmaco-dynamic properties

At concentrations of 50 $mg.1^{-1}$ (or less) silver Sulfadiazine is active against > 95% of the strains of many bacterial species, including Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Proteus morganii, Staphylococcus aureus, and Staph, epidermidis. However, with Ps. Aeruginosa, in vitro sensitivity does not consistently predict therapeutic efficacy in experimentally infected burned rats. Emergence of silver Sulfadiazine resistant strains has been reported (see below). The susceptibility of bacteria to silver Sulfadiazine is not related to their sulfonamide susceptibility.

The drug is also active against candida adbicans and certain other fungi, dermatophytes, and Herpesvirus hominis.

Daily application of silver Sulfadiazine cream offers a significantly better protection against bacterial colonization of human burn wounds than application every three or

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four days. The efficacy is a higher against colonization than against established infection. There is no systemic antibacterial efficacy.

5.3 Pre-clinical safety data

In mice, the $LD_{90\text{-}100}$ within 24 hours was ≥ 550 $mg.kg^{-1}$ when given by a single intraperitoneal injection. Oral or subcutaneous administration of 1050 $mg.kg^{-1}$ per day during 30 days did not result in acute or subacute toxicity or pathological changes in kidney, intestine, liver, or spleen. In rabbits, silver was deposited in the renal pyramids after daily application of Silver Sulfadiazine (5-15 $mg.kg^{-1}$) for 100 days, while no other structural damage to the kidney or renal impairment was found. Similar effects in humans have not been reported.

Burned mice given mixed Gram-negative infections and treated topically with Silver Sulfadiazine cream had a lower total white blood cell count, a lower percentage of actively phagocytosing polymorphonuclear leukocytes, and a reduced bactericidal capacity, as compared with cream-base treated controls.

Silver Sulfadiazine is not mutagenic in a mutagenicity assay using *Salmonella typhimurium*. There are not published observations of mutagenicity or teratogenicity in animals or man.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Chlorocresol	BP 2019	15.00 mg
White soft paraffin	BP 2019	750.00 mg
Light liquid paraffin	BP 2019	750.00 mg
Cetomacrogol-1000	BP 2019	300.00 mg
Mono basic sodium phosphate	BP 2019	15.00 mg
Propyl paraben	BP 2019	5.100 mg
Methyl paraben	BP 2019	15.00 mg
Cetostearyl alcohol	BP 2019	1.200 g
Purified water	BP 2019	q.s.

6.2 Incompatibilities

None reported

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Store under normal storage conditions (15°C to 30°C).
Protect from light.
Keep all medicines out of reach of children.

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6.5 Nature and Contents of Container

100 gram Lami Jar and flower pot type white HDPE cap with piercing spoke is packed in a unit Jar. Such sleeves packed in 5 ply shipper. Each shipper is sealed with BOPP tape. Each shipper is labelled with shipping marks.

ANIL K. PANDEY
DIRECTOR

Date :
Director of the manufacturer
(Signature, Full name, Stamp)

AGOG PHARMA LTD. VASAI

ANIL K. PANDEY
DIRECTOR

Date :
Director of applicant company
(Signature, Full name, Stamp)

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