SILVER SULFADIAZINE - silver sulfadiazine cream
Keltman Pharmaceuticals Inc.

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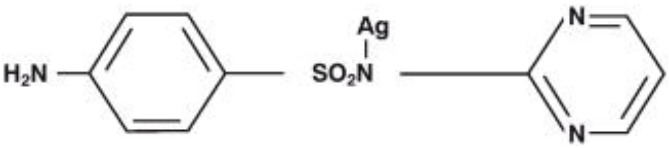
silver sulfadiazine 1% cream

DESCRIPTION

Silver sulfadiazine 1% cream is a soft, white, water-miscible cream containing the antimicrobial agent silver sulfadiazine in micronized form, which has the following structural formula:



Each gram of silver sulfadiazine 1% cream contains 10 mg of micronized silver sulfadiazine. The cream vehicle consists of CETYL ALCOHOL, ISOPROPYL MYRISTATE, POLYOXYL 40 STEARATE, PROPYLENE GLYCOL, WATER, STEARYL ALCOHOL, SODIUM HYDROXIDE, SORBITAN MONOOLEATE, PETROLATUM, METHYLPARABEN. SILVADENE Cream 1% (silver sulfadiazine) spreads easily and can be washed off readily with water.

CLINICAL PHARMACOLOGY

Silver sulfadiazine has broad antimicrobial activity. It is bactericidal for many gram-negative and gram-positive bacteria as well as being effective against yeast. Results from *in vitro* testing are listed below.

Sufficient data have been obtained to demonstrate that silver sulfadiazine will inhibit bacteria that are resistant to other antimicrobial agents and that the compound is superior to sulfadiazine.

Studies utilizing radioactive micronized silver sulfadiazine, electron microscopy, and biochemical techniques have revealed that the mechanism of action of silver sulfadiazine on bacteria differs from silver nitrate and sodium sulfadiazine. Silver sulfadiazine acts only on the cell membrane and cell wall to produce its bactericidal effect.

Results of In Vitro Testing with Silvadene® Cream 1% (silver sulfadiazine) Concentration of Silver Sulfadiazine Number of Sensitive Strains/Total Number of Strains Tested

Genus & Species	50 µg/mL	100 µg/mL
Pseudomonas aeruginosa	130/130	130/130
Xanthomonas (Pseudomonas) maltophilia	7/7	7/7
Enterobacter species	48/50	50/50
Enterobacter cloacae	24/24	24/24
Klebsiella species	53/54	54/54
Escherichia coli	63/63	63/63
Serratia species	27/28	28/28
Proteus mirabilis	53/53	53/53

Morganella morganii	10/10	10/10
Providencia rettgeri	2/2	2/2
Providencia species	1/1	1/1
Proteus vulgaris	2/2	2/2
Citrobacter species	10/10	10/10
Acinetobacter calcoaceticus	10/11	11/11
Staphylococcus aureus	100/101	100/101
Staphylococcus epidermidis	51/51	51/51
β-Hemolytic *Streptococcus*	4/4	4/4
Enterococcus species	52/53	53/53
Corynebacterium-diphtheriae	2/2	2/2
Clostridium perfringens	0/2	2/2
Candida albicans	43/50	50/50

Silver sulfadiazine is not a carbonic anhydrase inhibitor and may be useful in situations where such agents are contraindicated.

INDICATIONS AND USAGE

Silver sulfadiazine 1% cream 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.

CONTRAINDICATIONS

Silver sulfadiazine 1% cream 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, Silver sulfadiazine 1% cream 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.

WARNINGS

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 superinfection is low.

The use of Silver sulfadiazine 1% cream in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.

PRECAUTIONS

General

If hepatic and renal functions become impaired and elimination of drug decreases, accumulation may occur and discontinuation of Silver sulfadiazine 1% cream should be weighed against the therapeutic

benefit being achieved.

In considering the use of topical proteolytic enzymes in conjunction with Silver sulfadiazine 1% cream, the possibility should be noted that silver may inactivate such enzymes.

Laboratory Tests

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term dermal toxicity studies of 24 months' duration in rats and 18 months' in mice with concentrations of silver sulfadiazine three to ten times the concentration in Silver sulfadiazine 1% cream revealed no evidence of carcinogenicity.

Pregnancy

Teratogenic Effects.

Pregnancy Category B. A reproductive study has been performed in rabbits at doses up to three to ten times the concentration of silver sulfadiazine in SILVADENE Cream 1% and has revealed no evidence of harm to the fetus due to silver sulfadiazine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly justified, especially in pregnant women approaching or at term. (See **CONTRAINDICATIONS**.)

Nursing Mothers

It is not known whether silver sulfadiazine is excreted in human milk. However, sulfonamides are known to be excreted in human milk, and all sulfonamide derivatives are known to increase the possibility of kernicterus. Because of the possibility for serious adverse reactions in nursing infants from sulfonamides, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

Of the total number of subjects in clinical studies of Silver sulfadiazine 1% 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. (See **CONTRAINDICATIONS**.)

ADVERSE REACTIONS

Several cases of transient leukopenia have been reported in patients receiving silver sulfadiazine therapy.[1,2,3] Leukopenia associated with silver sulfadiazine administration is primarily characterized by decreased neutrophil count. Maximal white blood cell depression occurs within 2 to 4 days of initiation of therapy. Rebound to normal leukocyte levels follows onset within 2 to 3 days. Recovery is not influenced by continuation of silver sulfadiazine therapy. An increased incidence of leukopenia has

been reported in patients treated concurrently with cimetidine.

Other infrequently occurring events include skin necrosis, erythema multiforme, skin discoloration, burning sensation, rashes, and interstitial 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-Johnson syndrome and exfoliative dermatitis; gastrointestinal reactions; hepatitis and hepatocellular necrosis; CNS reactions; and toxic nephrosis.

DOSAGE AND ADMINISTRATION

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 SILVADENE Cream 1% (silver sulfadiazine) is applied under sterile conditions. The burn areas should be covered with Silver sulfadiazine 1% cream 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.

Treatment with Silver sulfadiazine 1% cream should be continued until satisfactory healing has occurred, or until the burn site is ready for grafting. The drug should not be withdrawn from the therapeutic regimen while there remains the possibility of infection except if a significant adverse reaction occurs.

HOW SUPPLIED

Silver sulfadiazine 1% creamis supplied by **Keltman Pharmaceuticals Inc.** as follows:

NDC	Strength	Quantity/Form	Color	Source Prod. Code
68387-450-01	10 mg/1 g	50 Grams in a Jar	white to off-white	00591-0810

REFERENCES

1. Caffee F, Bingham H. Leukopenia and silver sulfadiazine. J Trauma. 1982;22: 586–587.
2. Jarret F, Ellerbe S, Demling R. Acute leukopenia during topical burn therapy with silver sulfadiazine. Amer J Surg. 1978;135:818–819.
3. Kiker RG, Carvajal HF, Micak RP, Larson DL. A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children. J Trauma. 1977; 17:835–836.

Prescribing Information as of July 2003.

Manufactured for Watson Laboratories, Inc.
Corona, CA 92880 USA
Manufactured by Dr. Reddy's Laboratories Louisiana, LLC
Shreveport, LA 71106

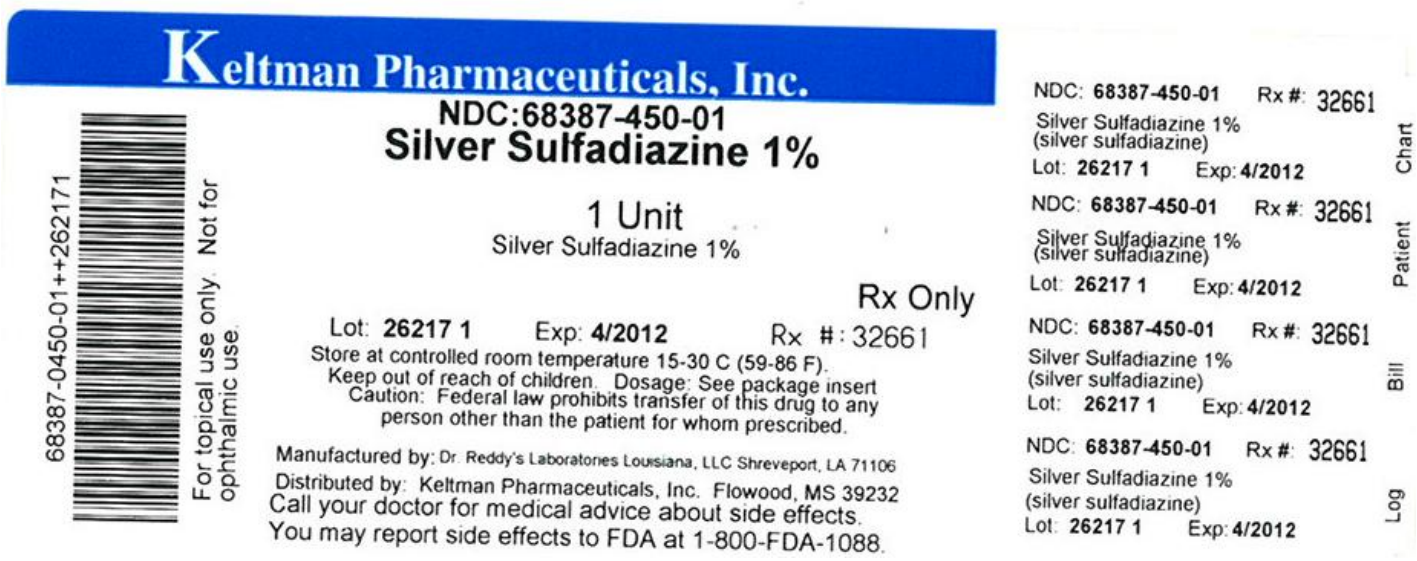
This Product was Repackaged By Sandhills Packaging For:

Keltman Pharmaceuticals Inc.
1 Lakeland Square, Suite A
Flowood, MS 39232
United States

Package Label - Principal Display Panel – 1% cream

NDC 68387-450-01

Rx Only



SILVER SULFADIAZINE

silver sulfadiazine cream

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68387-450(NDC:00591-0810)
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SILVER SULFADIAZINE (UNII: W46JY43EJR) (SILVER SULFADIAZINE - UNII:W46JY43EJR)	SILVER SULFADIAZINE	10 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
CETYL ALCOHOL (UNII: 936JST6JCN)	
ISOPROPYL MYRISTATE (UNII: 0RE8K4LNJS)	
POLYOXYL 40 STEARATE (UNII: 13A4J4NH9I)	

PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
STEARYL ALCOHOL (UNII: 2KR89I4H1Y)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
SORBITAN MONOOLEATE (UNII: 06XEA2VD56)	
PETROLATUM (UNII: 4T6H12BN9U)	
METHYLPARABEN (UNII: A2I8C7HI9T)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68387-450-01	50 g in 1 JAR		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA018578	03/10/2007	

Labeler - Keltman Pharmaceuticals Inc. (362861077)

Establishment

Name	Address	ID/FEI	Business Operations
Sandhills Packaging		825138717	repack

Revised: 9/2010 Keltman Pharmaceuticals Inc.