SILVEROL®

CREAM

Composition

Active Ingredient
Silver sulfadiazine (micronized) 1%

Other Ingredients
Paraffin oil, propylene glycol, cestostearyl alcohol, glyceryl monostearate, glyceryl monostearate self emulsifying, polysorbate 60 (tween 60), polysorbate 80 (tween 80), methylparaben, purified water.

Mechanism of Action
Silverol is a topical preparation with a broad antimicrobial activity, used for the treatment of burns. It is bactericidal for many Gram-positive and Gram-negative bacteria, as well as against yeasts, fungi and viruses.

Silver sulfadiazine exerts its effect on the cell membrane and cell wall. Silver is slowly released from the preparation in concentrations that are selectively toxic to bacteria. Both silver and sulfadiazine are active. Silverol is not a carbonic anyhydrase inhibitor. Acidosis has not been reported, so that it may be of particular value in treating pediatric burn patients.

While less than 1% of the silver content is absorbed, up to 10% of the sulfadiazine may be absorbed. Serum concentrations of 10-20 μg/ml have been reported when extensive areas were involved. The micronized formulation permits easy spreading on application, and exposes a large surface of the drug to the wound.

Indications
Antimicrobial preparation for local treatment of burns, infected pressure sores and leg ulcers.

Contraindications
Known hypersensitivity to silver sulfadiazine or to any other ingredient of the preparation.

Because sulfonamide therapy is known to increase the possibility of kernicterus, Silverol 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
Sensitization to topically applied silver sulfadiazine is rarely predicted or proven by patch testing. Caution should be exercised in the use of Silverol cream in individuals who have previously shown sensitization reactions to sulfonamides.
Silverol may be hazardous in individuals with glucose-6-phosphate-dehydrogenase deficiency, as hemolysis may occur.

In patients with extensive burn areas of the body, the following should be taken into consideration:
(a) complete blood counts may be required prior to and weekly during treatment to detect blood dyscrasias in this patient group; therapy should be discontinued if a significant decrease in the count of any formed blood elements occurs.
(b) considerable amount of silver sulfadiazine is absorbed. Serum concentrations of silver sulfadiazine may approach adult therapeutic levels (8 to 12 mg %). Therefore it is recommended to monitor serum sulfa concentrations. Particular attention must be paid to adequate fluid intake and acid base balances, and renal function should be carefully monitored and urine should be checked for sulfa crystals.
   Use of Silverol cream may delay separatin of burn eschar and may alter the appearance of burn wounds.
   Sulfonamides may precipitate an acute attack of porphyria.

Use in Pregnancy
A reproduction study has been performed in rabbits at doses up to 3-10 times the concentration of silver sulfadiazine present in the cream, 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 only be used during pregnancy in badly burned pregnant women if the benefit to the mother outweighs the risk to the foetus. Silverol cream should not be used when the patient is near term since sulfonamide therapy is known to increase the possibility of kernicterus (see Contraindications).

Use in Breastfeeding
It is not known whether silver sulfadiazine cream is excreted in human milk. However, sulfonamides are known to be excreted in human milk (15-35% of that in serum), 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 consideration the importance of the drug to the mother.

Use in Pediatrics
Safety and effectiveness in children and infants have not been established (see also Contraindications).

Adverse Reactions
Skin and Subcutaneous Tissue Disorders
Common: application site rash, including eczema and contact dermatitis may occur in about 2% of patients; pruritus.
Rare: there is evidence that in large area burn wounds and/or after prolonged application, systemic absorption of silver may occur causing clinical argyria.
Blood and Lymphatic Tissue

Several cases of transient leucopenia have been reported in patients receiving silver sulfadiazine therapy (up to 3-5% of patients). Leucopenia 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 leucopenia has been reported in patients treated concurrently with cimetidine (see Drug Interactions).

Renal and Urinary Disorders

Very rare: renal failure

Other

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, leucopenia, and hemolytic anemia; dermatologic and allergic reactions, including Stevens-Johnson syndrome and exfoliative dermatitis; photosensitivity, gastrointestinal reactions; hepatitis and hepatocellular necrosis; CNS reactions; and toxic nephrosis.

Other infrequently occurring events include skin necrosis, erythema multiforme, skin discoloration, burning sensation, rashes, and interstitial nephritis.

Fungal colonization in and below the eschar may occur concomitantly with reduction of bacterial growth. However, fungal dissemination is rare.

Precautions

If hepatic or renal function become impaired and elimination of drug decreases, accumulation may occur. Discontinuation should be weighed against any therapeutic benefit being achieved.

Reduction in bacterial colonization has caused delayed separation, in some cases necessitating escharotomy in order to prevent contracture.

Leucopenia 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 Silverol 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.

Drug Interactions

Silverol/Proteolytic Enzymes: In considering the use of topical proteolytic enzymes in conjunction with silver sulfadiazine, it should be noted that there is a possibility that the silver may inactivate such enzymes.

Silverol/Oral Hypoglycemic Agents/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.
Silverol/Cimetidine: In patients with large area burns, it has been reported that co-
administration of cimetidine may increase the incidence of leucopenia.

Laboratory Tests
Absorption of the propylene glycol vehicle has been reported to affect serum
osmolality, which may affect the interpretation of laboratory tests.

Directions for Use
Silverol should be applied in a layer approximately 3-5 mm thick with a sterile, gloved
hand or spatula, to completely cover the burn area. Ordinarily, blisters are not opened,
but loose tissue is generally removed prior to application.

After application of Silverol, the wound should either be left exposed or covered with
a fine mesh gauze and an elastic mesh bandage.

The exposure method is preferable in some patients (such as children) and for certain
parts of the body (face, genitalia, etc.). When the wound is exposed, Silverol should be
reapplied at about 12-hour intervals, or more frequently if the medication is rubbed off
on the bedding. When dressings are used, they should be changed daily or on
alternate days. Use of dressings serves to press the medication firmly against the
wound, helps keep the area moist, reduces evaporative water loss and prevents
drying/caking of the medication.

Silverol dressings can usually be left in place for about 48 hours during the first
2 weeks post burn. Subsequently, necrotic tissue undergoes proteolytic decomposition,
producing considerable exudate which dilutes the drug and necessitates more frequent
dressing changes. When feasible, patients should be bathed daily as an aid in
debridement. A whirlpool bath is particularly helpful, but patients may be bathed in bed
or in a shower.

With Silverol treatment, there will generally be an absence of infection, and
examination of the wound will reveal soft pliable eschars. These will separate
gradually, leaving a clear granulating surface. In partial-thickness burns, the generating
epithelium often appears in about 2 weeks, and burns initially classified as full-
thickness injuries often heal within 5 weeks without grafting.

In leg ulcers, Silverol should be applied followed by an absorbent gauze dressing and
a support bandage, e.g. 10 cm elastic bandage. Care should be taken not to spread
Silverol on to non-ulcerated skin, and it should not be used on every wet ulcer. The
dressing should be changed at least 3 times a week, and desloughing and cleansing
should be carried out at the same time.

Any Silverol remaining at the end of treatment should be discarded.

Treatment with Silverol 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 the possibility of infection remains, unless a significant side
effect occurs.
**Pharmaceutical Precautions**

The container should be stored in a cool place, away from light. A separate container of Silverol should be reserved for each patient. Any remaining cream should be discarded on the completion of treatment.

**Presentation**

Aluminium tubes of 50 g.

**Registration Number**

020 56 20515 00.

**Manufacturer**

Teva Pharmaceutical Industries Ltd
P.O.Box 3190, Petach Tikva
For
Abic Ltd
P.O.Box 8077, Kiryat Nordau, Netanya