Prescribing Information for a Registered Medical Practitioner

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Silver Sulfadiazine, Chlorhexidine Gluconate and Recombinant Human Epidermal Growth Factor Cream

SLVRGEN® सिलवरजेन®

1 NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT

SLVRGEN® is a Human Epidermal growth factor-based cream produced by recombinant DNA technology in combination with silver sulfadiazine and chlorhexidine gluconate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition	
Each gram contains	
Silver Sulfadiazine IP	1% w/w
Chlorhexidine Gluconate Solution IP	0.2% w/w
Liquid light paraffin IP	10% w/w
Pemulen TR - 1 NF	0.5% w/w
Carbopol Ultrez NF	1.3% w/w
Sodium Methylparaben IP	0.18% w/w
Sodium Propylparaben IP	0.02% w/w
Mannitol IP	5.0% w/w
r-Human Epidermal Growth Factor	10µg/g
20% Triethanolamine IP	q.s. to adjust the pH to 6.2 - 6.3
Purified Water IP	78%

3 PHARMACEUTICAL FORM

Topical Cream

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Primarily used for the treatment of first and second-degree burns.
- Also indicated in other skin ulcers like abrasions, incisions, minor cuts and wounds.

4.2 Posology and Method of Administration

Burns:

- The "Rule of 9's" is commonly used to estimate the burned surface area in adults
- The burn wounds should be cleaned and **SLVRGEN®** cream applied over all the affected areas to a depth of 3 to 5 mm.
- One technique is to apply the cream 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.
- **SLVRGEN®** should be re-applied at least every 24 hours.

Hand Burns and Finger Injuries:

- One recommended method, which has been found successful, is to apply **SLVRGEN®** to the burn and the whole hand.
- The patient should be encouraged to move the hand and fingers. The dressing should be changed every three days

According to WHO guidelines[1] for Hand burns

- Cover the hands with topical cream and place them in loose polythene gloves or bags secured at the wrist with a crepe bandage.
- Elevate the hands for the first 48 hours, and then start hand exercises.
- At least once a day, remove the gloves, bathe the hands, inspect the burn and then reapply topical cream and the gloves

4.3 Contraindications

Silver sulfadiazine cream is contraindicated in patients known to be hypersensitivity to silver sulphonamide or to other components of the preparation such as cetyl alcohol or propylene glycol[2]. Because sulphonamide therapy is known to increase the possibility of kernicterus, silver sulphadiazine cream should not be used in pregnant women at term, in premature infants or in infants during the first months of life. It should not be used if hepatic and renal functions become impaired or if the condition of porphyria is suspected[3].
Recombinant human Epidermal Growth Factor is generally well tolerated.

4.4 Special Warnings and Precautions for use:

- Caution is required in patients known to be sensitive to silver sulphadiazine, which induce haemolytic anaemia in individuals known to have glucose-6-phosphate dehydrogenase deficiency and concomitant use with topical proteolytic enzymes[3].
- Use of silver sulfadiazine cream may delay separation of burn eschar (falling away of dead skin) and may alter the appearance of the burn wounds[3].

4.5 Interactions with Other Medicinal Products and other forms of interaction

- Cimetidine: In patients with large area burns, it has been reported that coadministration of cimetidine may increase the incidence of leukopenia[6]
- Sodium nitrite: Using sodium nitrite together with silver sulfadiazine topical may increase the risk of methemoglobinemia, a condition that can lead to oxygen deprivation in tissues and vital organs due to reduced oxygen-carrying capacity of the blood[7]
- Collagenase or Papain or Sutilains: Concurrent use of proteolytic enzymes with silver sulfadiazine is not recommended since heavy metal salts may inactivate the enzymes[3].

4.6 Pregnancy and Lactation

The safe use of silver sulfadiazine has not been established in pregnancy and lactation.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effect of **SLVRGEN®** on the ability to drive and use machines has been performed.

4.8 Adverse Events

Adverse events may occur such as Pain, Itching, Rash, Skin irritation, Itching, fever, Abdominal Pain, Headache. Leukopenia and Silver poisoning by **SLVRGEN®** was not observed during the study. However, Leukopenia can be observed in patients treated with silver sulfadiazine[3]. Silver poisoning, like Argyria which is a rare cutaneous discoloration caused by the up take of silver or various compounds containing silver[10]

4.9 Overdose

In case treatment with silver sulfadiazine cream involves prolonged administration and/or large burned surfaces, considerable amount of silver sulfadiazine is absorbed. When an excessive absorption occurs, it is important to optimally maintain fluid balance not only to prevent dehydration but also to avoid the possibility of renal impairment[11]

Absorbed silver has not been reported as the cause of serious toxic manifestations in recommended doses.

4.10 Pre-Clinical & Clinical Trial Experience

Pre-Clinical studies were performed on Wistar rats (48 Male and 48 females), concluded that the topical formulation cream was the best formulation to be used for burn patients

In a clinical trial: Total of 450 Patients with superficial and partial thickness burn were recruited at 11 clinical centres. The male & female distribution in the **SLVRGEN®** group was 186 and 114 respectively while in the reference group was 86 male and 64 females. Overall 272 male and 178 females participated in study. The presented data suggests that **SLVRGEN®** is an effective antimicrobial with added epithelial growth factor which accelerates burn wound healing. The application of **SLVRGEN®** to burns has many advantages over topical treatment with Silver sulfadiazine + CHG, including the significant decrease in the level of pain, follow-up times, time of wound closure with lesser cost of treatment.

The combination of silver sulfadiazine, chlorhexidine and recombinant epidermal growth factor in **SLVRGEN®** offers the advantage of broad spectrum of activity, synergistic antimicrobial action, a very low potential for the development of resistant strains and early healing of wound due to increased rate of Cell Proliferation, Maturation and Epithelization.

4.11 Post-Marketing Experience

- A prospective multicenter study to evaluate the safety and efficacy of **SLVRGEN®** (rhEGF+ 1% Silver Sulfadiazine + 0.2% Chlorhexidine Gluconate) in comparison with commercially available (1% Silver Sulfadiazine + 0.2% Chlorhexidine Gluconate) cream in patients with superficial partial thickness burns (first and second-degree burns).
- In Test group a total of 225 patients were enrolled, 173 patients had complete wound closure, 39 patients had in between 80 to 100 % of closure and 14 patients had completed the closure of wound less than 80 %.
- In Reference group, a total of 75 patient were enrolled, 21 patients had complete wound closure, 17 patients had in between 80 to 100 % of closure and 15 patients had completed the closure of wound less than 80%. **SLVRGEN®** had lower pain scores than when compared to the other SSD treated groups.
- Overall, the most common complications observed were itching and pain. Local itching was reported in 42(14%) patients who received **SLVRGEN®** and 38(25%) patients who received reference group respectively (p<0.05).
- Pain as an adverse event i.e. increased intensity of pain from the baseline was found in 39 (13%) patients who received **SLVRGEN®** and 53(36%) patients who received reference group respectively.
- Fever associated with wound infection was reported in 17 (6%) patients who received **SLVRGEN®** and 29(19%) patients who received reference drug respectively.
- The basic purpose of physical therapy was to prevent the development of hypertrophic or keloid scars after treatment of the burns. Keloid scars were most commonly noted after deep second-degree burns. 2 patients in the **SLVRGEN®** treated group and 5 in the reference group treated experienced keloids in the limb, face, and neck region which were treated surgically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Silver sulfadiazine acts on the cell membrane and cell wall of microorganisms to produce its bactericidal effect. Silver is slowly released from the preparation in concentrations that are selectively toxic to bacteria. Silver also damages the DNA of the bacterial cell. Sulfadiazine, like other sulphonamides, inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Thus, silver and sulfadiazine together produce a synergistic action on the microorganisms.

Chlorhexidine gluconate is adsorbed onto the cell walls of microorganisms, which causes leakage of intracellular components. At low concentrations, chlorhexidine gluconate is bacteriostatic; at higher concentrations, it is bactericidal.

Epidermal Growth Factor (EGF) peptide induces cellular proliferation through the EGF receptor, which has a tyrosine kinase cytoplasmic domain, a single transmembrane domain and an extracellular domain involved in EGF binding and receptor dimerization. The proliferative effects of EGF are signaled through several pathways. Binding of EGF results in EGF receptor dimerization, autophosphorylation of the receptor, and tyrosine phosphorylation of other proteins. EGF receptor activates MAP kinase pathway, ultimately causing phosphorylation of transcription factors that contribute to proliferation.

5.2 Pharmacokinetic Properties

The degree of silver sulfadiazine uptake will significantly depend upon the surface area of the wound and the dosing regimen. No silver deposits have been observed in renal tissues of partial and full thickness burn patients treated with extensive amounts of topical silver sulfadiazine for 3 weeks. Sulfadiazine is excreted in the urine[12].

Chlorhexidine is poorly absorbed through the intact skin; systemic absorption may occur from the broken skin. Chlorhexidine is metabolized in the liver; it is excreted largely unchanged in feaces through the bile[13].

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Liquid light paraffin IP
Pemulen TR - 1 NF
Carbopol Ultrez NF
Mannitol IP
20% Triethanolamine IP

6.2 Incompatibilities

No incompatibility studies have been conducted with **SLVRGEN®**

6.3 Shelf Life

The shelf life of **SLVRGEN®** is indicated on the label and carton of the product

6.4 Special Precautions for Storage

SLVRGEN® should be protected from light and stored in a cool and dry place. Keep the cap tightly closed after use. After completion of treatment, any cream remaining in the tube should be discarded.
DO NOT FREEZE, DISCARD IF FROZEN. Do not use the cream after expiry date shown on tube and carton. Keep out of reach of children

7. PRESENTATION

SLVRGEN® is available in Tubes of 15 gms and 30 gms.

References

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10 Frederick W. Fuller, MD the Side Effects of Silver Sulfadiazine Journal of Burn Care & Research Volume 30, Number 3
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13 Product monograph prchlorhexidine Chlorhexidine Gluconate Oral Rinse, 0.12% w/v House Standard, Euro-Pharm International Canada Inc. 9400 Boul. Langelier Montreal, Quebec H1P 3H8

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Lead Innovation

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