SLVRGEN®

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

BHARAT BIOTECH
Lead Innovation

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

Name of the product: Recombinant Human Epidermal Growth Factor, Silver Sulfadiazine & Chlorhexidine Gluconate Cream

Strength:
Each gram contains:
Silver Sulfadiazine IP ..... 1% w/w
Chlorhexidine Gluconate Solution IP ..... 0.2% w/v
r-Human Epidermal Growth Factor ..... 10 µg/g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each gram contains:
Silver Sulfadiazine IP ..... 1% w/w
Chlorhexidine Gluconate Solution IP ..... 0.2% w/v
r-Human Epidermal Growth Factor ..... 10 µg/g
Sodium Methyl Paraben IP ..... 0.18% w/w
Sodium Propyl Paraben IP ..... 0.02% w/w
Excipients ..... q.s

3. PHARMACEUTICAL FORM:

Topical Cream

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

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

4.2 Posology and method of administration:

Burns:

- 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 is then enclosed in a clear plastic bag or glove, which is then closed at the wrist. The patient should be encouraged to move the hand and fingers. The dressing should be changed every three days or when an excessive amount of exudate has accumulated in the bag.

4.3 Contraindications:

Because sulfonamide therapy is known to increase the possibility of kernicterus, **SLVRGEN®** should not be used in pregnant females at term, in premature infants, or in newborn infants in the first month of life.

Recombinant Human Epidermal Growth Factor is generally well tolerated. However the product should not be used on patients with a known sensitivity to any of its components.

4.4 Special warnings/precautions:

Sensitization to topically applied silver sulfadiazine is rarely predicted or proven by patch testing. Caution should be exercised in the use of **SLVRGEN®** in individuals who have previously shown sensitization reactions to sulfonamides.

SLVRGEN® should be used with caution on patients with a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency as hemolysis may occur.

When treatment with **SLVRGEN®** involves prolonged administration and/or large burned surfaces, considerable amounts of silver sulfadiazine are absorbed. Serum concentration of silver sulfadiazine may approach adult therapeutic levels (8 to 12 mg%).

SLVRGEN® should be used with caution if hepatic or renal function is significantly impaired.

Leukopenia has been reported following the use of silver sulfadiazine, especially on patients with large area burns. This may be a drug-related effect, and often occurs 2 to 3 days after treatment has commenced. It is usually self-limiting and therapy with silver sulfadiazine 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.

4.5 Interaction with other medicinal products

- **Cimetidine**
  In patients with large area burns, it has been reported that coadministration of cimetidine may

increase the incidence of leukopenia.

- **Collagenase or Papain or Sutilains**
  Concurrent use of proteolytic enzymes with silver sulfadiazine is not recommended since heavy metal salts may inactivate the enzymes.

- **Oral hypoglycemic agents and 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.

4.6 Pregnancy and lactation:

The safe use of silver sulfadiazine has not been established in pregnancy. **SLVRGEN®** should only be used in badly burned pregnant women if the benefit to the patient outweighs the risk to the fetus. Silver sulfadiazine should not be used when the patient is near term (see Contraindications).

4.7 Effect on the ability to drive and use machines:

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

4.8 Undesirable effects:

ADVERSE EFFECTS
Leukopenia:
In patients with large area burns, silver sulfadiazine treatment has been reported to cause a rash in 2 to 5% of patients. Moderate, and usually transient, leukopenia has been reported in up to 3 to 5% of patients and occurs within 48 to 72 hours after therapy has commenced, and generally occurs in patients with at least 30% burns. It is usually self-limiting and the leukocyte count is normalized within 2 to 3 days regardless of whether treatment with silver sulfadiazine is continued or terminated. Caution should be exercised in individuals who have previously shown a sensitization to sulfonamides, however sensitization to topically applied silver sulfadiazine is rarely predicted or proven by patch testing.

Sulfonamide:
During the treatment of burns over large body surfaces (greater than 20% body surface area), significant amounts of silver sulfadiazine are systematically absorbed. Therefore, it is possible that any adverse reactions associated with sulfonamides may occur.

Recombinant Human Epidermal Growth Factor:
Recombinant Human Epidermal Growth Factor has proven low reactogenicity and is well tolerated.

4.9 Overdose:
Symptoms and Treatment:
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Silver sulfadiazine acts on the cell membrance 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.

SPECTRUM AND RESISTANCE
Silver sulfadiazine is a broad-spectrum antimicrobial agent. It is bactericidal for many gram-negative and gram-positive bacteria as well as being effective against yeast. Micro-organisms suspectible to the action of silver sulfadiazine include sensitive strains of Pseudomonas aeurginosa, Pseudomonas maltophilia, Enterobacter spp., Enterobacter cloacae, Klebsiella spp., E.coli, Serratioa spp., Providencia mirabilis, Morganella morganii, Proteus rettgeri, Proteus vulgaris, Providencia spp., Citrobacter spp., Acinetobacter calcoaceticus, Staphylococcus aureus, Staphylococcus epidermidis, ß-hemolytic Streptococcus, Enterococcus

spp., Corynebacterium diphtheriae, Clostridium perfringens and Candida albicans.

Chlorhexidine is an anti-microbial agent effective against a wide range of gram-positive and gram-negative bacteria at a concentration of 0.2%. It is also effective against some viruses and fungi. It has rapid bactericidal activity against a wide spectrum of non-sporing bacteria.

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.

5.2 Pharmacokinetic properties

Silver sulfadiazine does not get abosrbed to any significant extent into the systemic circulation even from the injured skin due to its higher molecular weight and thus, it can be safely used even in third degree burns. The degree of uptake will significantly depend upon the nature of the wound and the dosing regime. Absorbed silver has never been reported as the cause of serious toxic manifestations in recommended doses. 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.

Chlorhexidine is poorly absorbed through the intact skin. systemically absorbed from the broken skin, chlorhexidine is metabolized in the liver. It is excreted largely unchanged in faeces through the bile.

5.3 Pre-clinical safety data

Not Available

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:
Sodium Methyl Paraben
Sodium Propyl Paraben

6.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life:

The Expiry date of the **SLVRGEN®** is indicated on carton of the product.

6.4 Special precautions for storage:

SLVRGEN® should be stored in a Room Temperature (25°C ± 2°C). 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
Keep out of reach of children

6.5 Nature and contents of container:

SLVRGEN® is available in Tubes of 15 gms, 30 gms, 50 gms and 100 gms.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BHARAT BIOTECH Lead Innovation
Bharat Biotech International Limited situated
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal, Malkajgiri District, Telangana State, India, Pin: 500078.

8. MARKETING AUTHORISATION NUMBER
MF-977/08

9. DATE OF FIRST MARKETING AUTHORISATION
17 NOV 2008

10. DATE OF REVISION
June 2023