# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

SILVERDIN 1% Cream

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g cream contains:
**Active substance:**
Silver sulfadiazine 10 mg

**Excipients:**
Cetyl alcohol 40 mg
Methylparaben 3 mg
Propylene glycol 70 mg
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Cream.
White, odorless cream with soft consistency.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

It is indicated
- In the prophylaxis and treatment of burns infected with Gram-positive and Gram-negative microorganisms susceptible to silver sulfadiazine.
- As an adjunct to short-term treatment of infection in leg ulcers and pressure sores.
- As an adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions.
- As a conservative in fingertip injuries where there is partial loss of the fleshy part of the finger, nail loss and/or distal phalanx.

### 4.2 Posology and method of administration

For topical application. Not suitable for ocular administration.
**Posology/frequency and duration of administration:**

**In burns:**
After the wound or burn area is cleaned according to appropriate hygienic rules, SILVERDIN should be applied as a 3-5 mm thick layer.
It is recommended to apply with sterile gloves and/or sterile spatula. Where necessary, the cream should be re-applied to any area from which it has been removed by patient activity.

In burns, SILVERDIN should be applied at least once a day. In cases where the exudate volume is high, it can be applied more frequently.

**In hand burns:**
After applying SILVERDIN to the burned area, the whole hand can be placed in a transparent

plastic bag or glove and closed from the wrist.
The patient should be encouraged to move the hand and fingers.
The dressing should be changed when an excessive amount of exudate has accumulated in the bag.

**Leg ulcers/Pressure sores:**
The cavity of the ulcer should be filled with SILVERDIN to a depth of at least 3-5 mm. As SILVERDIN cream can cause maceration of normal skin on prolonged contact, care should be taken to prevent spread onto non-ulcerated areas.

After SILVERDIN, an absorbent pad or gauze dressing should be applied. In addition, a pressure dressing can be applied if the ulcer wound requires it. The dressings should be changed daily in normal circumstances but for wounds which are less exudative, less frequent changes (every 48 hours) may be appropriate. Before applying SILVERDIN, the application area should be cleaned and foreign objects should be removed.
SILVERDIN cream is not recommended for use in leg or pressure ulcers that are very exudative.

**Finger-Tip injuries:**
After the bleeding of the wound has been stopped, SILVERDIN should be applied in a layer of 3-5 mm thickness. A conventional dressing may be used. Alternatively the finger of a plastic or unsterile surgical glove can be used and fixed in place with waterproof tape. Dressings should be changed every 2-3 days.

**Additional information on special populations:**

**Renal/Hepatic impairment:**
There is no special method of administration for this population. It should be used with caution in patients with severe renal or hepatic impairment.

**Pediatric population:**
There is no special method of administration for this population. It should not be used in premature infants and newborns less than 2 months of age.

**Geriatric population:**
There is no special method of administration for this population.

**4.3 Contraindications**
It is contraindicated
- In patients with known hypersensitivity to silver sulfadiazine and other ingredients of the medicine.
- In the last period of pregnancy as sulphonamides are known to increase the possibility of kernicterus,
- Premature infants and infants younger than two months of age.
- Co-administration of methenamine and sulphonamides is contraindicated due to crystal urea formation.

**4.4 Special warnings and precautions for use**
Long-term use of anti-infective may cause development of super-infection associated with organisms resistant to the anti-infective administered. Fungal invasion in and below the eschar of wound may occur. However, clinical data show that the possibility of fungal superinfection is very

low.

SILVERDIN should be used with caution in patients with respiratory insufficiency, severe renal or hepatic impairment. In cases when the drug elimination is reduced as a result of renal or hepatic failure, accumulation may occur; decision should be made as to whether continuing with SILVERDIN therapy or not considering the therapeutic benefit aimed.

Absorption of silver sulfadiazine depends on size of the administration site and degree of tissue damage. Adverse reactions related to sulphonamides may develop though only a few were reported. Some of the reactions associated with sulphonamides include: blood disorders including agranulocytosis, aplastic anemia, thrombocytopenia, leucopenia and hemolytic anemia; dermatological and allergic reactions including life-threatening cutaneous reactions such as Stevens-Jonhson's Syndrome (SJS), toxic epidermal necrolysis (TEN) and exfoliative dermatitis; gastrointestinal reactions; hepatitis and hepatocellular necrosis; central nervous system reactions and toxic nephrosis.

There is a potential cross sensitivity between silver sulfadiazine and other sulfonamides. If allergic reactions occur due to treatment, a decision should be made whether to continue treatment, taking into account the potential hazards of the allergic reaction.
The use of silver sulfadiazine in patients with glucose-6-phosphate dehydrogenase-deficient may be hazardous as hemolysis may occur. It should be used with caution in these patients.

In cases for which co-administration of topical proteolytic enzymes and SILVERDIN is considered, it should be taken into consideration that the silver it contains may inactivate such enzymes.

SILVERDIN use may delay eschar separation and may change the appearance of burn injuries.

For treatment of burn wounds covering an extensive surface of body, serum sulfa concentrations can reach adult therapeutic levels (8-12 mg%). Therefore, monitoring of serum sulfa concentrations is recommended in such patients. Renal function should be closely monitored and presence of sulfa crystal in urine should be checked. It has been reported that propylene glycol absorption affects serum osmolality and laboratory test results.

1 g SILVERDIN contains 40 mg cetyl alcohol. Cetyl alcohol may cause local skin reactions (such as contact dermatitis).
1 g SILVERDIN contains 3 mg methylparaben. Methylparaben may cause (probably delayed) allergic reactions.
1 g SILVERDIN contains 70 mg propylene glycol. Propylene glycol may cause skin irritation.

**4.5 Interaction with other medicinal products and other forms of interaction**
Silver in SILVERDIN may inactivate enzymatic debriding agents, their concomitant use may not be appropriate.

When applied to large surfaces, serum sulfadiazine may reach therapeutic levels and may interact particularly with oral hypoglycemic drugs, phenytoin. It is recommended to monitor blood levels of the hypoglycemic drug and phenytoin as their effects may be potentiated when used together.
Urinary system antibacterial agent methenamine breaks down into ammonia first and then formaldehyde which may form an insoluble precipitate in acid urine with sulphonamides. Co-administration of methenamine and sulphonamides is contraindicated due to increased risk of crystallurea formation.

Concurrent application of papain and silver salt-containing formulations such as silver sulfadiazine may result in the inactivation of the enzymatic debriding action of papain. It results in decrease of effectiveness of papain-mediated chemical debridement.

## 4.6 Pregnancy and lactation

**General Recommendation**
Pregnancy category: C

**Women of child-bearing potential/Birth control (Contraception)**
There is not any data as to its effects on contraception.

**Pregnancy**
As all sulphonamides increase the risk of kernicterus, SILVERDIN should not be used the last period of pregnancy.

A reproductive study has been performed in rabbits at doses up to 3-10 times the concentration of silver sulfadiazine in SILVERDIN and has revealed no evidence of harm to the fetus due to silver sulfadiazine. However, since there are no such studies on pregnant women and animal reproduction studies do not provide the same results in humans, it should only be used in pregnant women when absolutely necessary. It is not safe to use towards the end of pregnancy. Caution should be taken when it is administered to pregnant women.

**Breastfeeding**
It is unknown whether SILVERDIN is excreted in breast milk or not. 15-35% of systemic sulfadiazine serum concentrations can be excreted in milk. As it is known that sulphonamides are excreted in milk and as all the sulphonamides increase the risk of kernicterus, caution should be taken for its use in breastfeeding women.

**Reproductive ability/Fertility**
There is no data on the effect on reproductive ability.

## 4.7 Effects on ability to drive and use machines
Negative effect on ability to drive and use machines was not reported.

## 4.8 Undesirable effects
Absorption of topically administered silver sulfadiazine depends on the area of the surface to be treated and the severity of the tissue damage. When it is applied on extensive areas, some systemic side effects may be observed.
Adverse effects are classified in line with the following descriptions within each system organ class:

Very common (>1/10);
Common (>1/100 to <1/10);
Uncommon (>1/1,000 to <1/100);
Rare (>1/10,000 to <1/1,000);
Very rare (<1/10,000),
Not known (cannot be estimated from the available data)

**Blood and lymphatic system disorders**
Not known: Agranulocytosis, aplastic anemia, glucose-6-phosphate dehydrogenase deficiency

anemia, hemolytic anemia, silver poisoning (argyrosis), thrombocytopenia, leucopenia (its co-administration with cimetidine was associated with incidence of leucopenia).

**Immune system disorders**
Rare: Hypersensitivity reactions.

**Metabolism and nutritional disorders**
Not known: Serum hyperosmolarity, water and electrolyte imbalance.

**Nervous system disorders**
Not known: Fever seizures.

**Gastrointestinal disorders**
Not known: Accumulation of silver in oral mucosa, pseudomembranous enterocolitis, toxic megacolon.

**Hepato-biliary diseases**
Not known: Hepatic necrosis, hepatitis.

**Skin and subcutaneous tissue disorders**
Common: Rash on application site including pruritus, eczema and contact dermatitis.
Rare: Burning sensation, color change on skin, erythema multiforme, skin necrosis.
Not known: Incomplete recovery of wounds, argyria, hyperpigmentation, erythroderma, exfoliative dermatitis, fungal infection, Stevens-Johnson's syndrome, toxic epidermal necrolysis.

**Renal and urinary tract disorders**
Rare: Interstitial nephritis.
Very rare: Renal impairment.
Not known: Crystalluria, nephrotoxicity.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

**4.9 Overdose**
Overdose is not expected with topical administration.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Topically administered sulphonamides
ATC code: D06BA01

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 silver sulfadiazine cream**

| | **Concentration of Silver Sulfadiazine Number of sensitive strains/Total number of strains tested** | |
|---|---|---|
| **Class/Species** | **50 mcg/ml** | **100 mcg/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 |
| *Acinobacter 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 | 0/2 |
| *Candida albicans* | 43/50 | 50/50 |

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

## 5.2 Pharmacokinetic properties

**General properties**

Absorption:

There is evidence that clinical argyria occurs as a result of systemic absorption of silver when applied to large surfaces and/or for long periods of time. Sulfadiazine diffuses easily into the wound and enters the circulation.

The extent of migration depends largely on the condition of the wound and the dose applied. Although silver is not absorbed systemically, sulfadiazine may be absorbed into the blood especially when the drug is applied to large areas and/or over prolonged periods of time. Studies conducted with radioactive silver sulfadiazine indicated that silver is not absorbed in topical applications.

Distribution:

Any amount of silver absorbed may remain in body for long periods of time especially in liver.

Serum sulphonamide level is directly proportional to the extent of burned areas and to the amount of cream applied. During prolonged treatment of burn wounds involving extensive areas of the body, pediatric serum sulphonamide levels may reach adult serum sulphonamide levels (8-12 mg/dl). Sulfadiazine concentrations as high as 9.1 mg/dl within 24 h of topical application were reported in the serum of severely burned patients receiving silver sulfadiazine.

Biotransformation:
Sulfadiazine is acetylated and oxidized in liver. Sulfadiazine is available in blood as acetyl derivative up to 40%.

Elimination:
Sulfadiazine is excreted unchanged via kidneys by 60%.
Half-life of the medicinal product is 10 hours and may extend up to 22 hours in anuric patients.

Linearity/Non-linearity:
Not applicable.

### 5.3 Preclinical safety data
In long-term dermal toxicity studies in rats for 24 months and in mice for 18 months, where silver sulfadiazine at level 3-10 times the concentration in SILVERDIN was applied, indication of carcinogenicity was not found.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Polysorbate 80
Polysorbate 60
Glycerin monostereate
Cetyl alcohol
Liquid paraffin
Methylparaben
Propylene glycol
Deionized water

### 6.2 Incompatibilities
SILVERDIN does not have any known incompatibility with any drug or substance.

### 6.3 Shelf life
48 months

### 6.4 Special precautions for storage
Store at room temperature below 25°C. Protect from light.

### 6.5 Nature and contents of container
- 40 g cream:

White, LDPE tube – white propylene cap.
Each cardboard box contains 1 tube of 40 g with foiled mouth.
- 400 g cream:

Grey, HDPE jar – black propylene cap and white – semi-opaque colored polyethylene stopper.

Each cardboard box contains 1 jar of 400 g.

**6.6 Special precautions for disposal and other handling**
Any unused material should be disposed according to local disposal regulations.

## 7. MARKETING AUTHORIZATION HOLDER

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## 7. MARKETING AUTHORIZATION NUMBER

126/19

## 8. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 30.06.1977
Date of last renewal : 14.01.2013

## 10. DATE OF REVISION OF THE TEXT