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

- For the prophylaxis and treatment of burn wounds 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 conservative management of finger-tip injuries where pulp, nail loss and/or partial loss of distal phalanx has occurred.

4.2 Posology and method of administration

To be applied topically. Not suitable for ocular administration.

Posology/frequency and duration of administration:

In burns
SILVERDIN should be applied as a layer with 3-5 mm thickness after the wound and burned area are cleaned in line with hygiene rules.
This application is best achieved 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.
In burns, SILVERDIN cream should be re-applied at least every 24 hours, or more frequently if the volume of exudate is large.

Hand burns
SILVERDIN cream can be applied to the burn and the whole hand 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 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 cream 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.

Application of SILVERDIN cream should be followed by an absorbent pad or gauze dressing, with further application of pressure bandaging as appropriate for the ulcer.
The dressings should normally be changed daily but for wounds which are less exudative, less frequent changes (every 48 hours) may be acceptable. Cleansing and debriding should be performed before application of SILVERDIN cream.
SILVERDIN cream is not recommended for use in leg or pressure ulcers that are very exudative.

Finger-Tip injuries
Hemostasis of the injury should be achieved prior to the application of a 3-5 mm layer of SILVERDIN cream. 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 adhesive 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 medicinal product.
- In pregnancy at or near term 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, the incidence of clinically reported fungal superinfection is low.

SILVERDIN should be used with caution in patients with respiratory insufficiency, severe renal or hepatic impairment. In cases when the medicinal product eliminated is reduced as a result of renal or hepatic impairment, 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 attributable to treatment with silver sulfadiazine occur, continuation of therapy must be weighed against the potential hazards of the particular allergic reaction.

The use of silver sulfadiazine cream in some cases of glucose-6-phosphate dehydrogenase-deficient patients 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, in such patients, it is important to monitor serum sulfa concentrations. 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.

In large-area burns where serum sulfadiazine levels may approach therapeutic levels, this can especially apply to oral hypoglycemic agents and to phenytoin. In the case of these drugs, it is recommended that blood levels should be monitored as their effects can be potentiated.

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 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is C.

Women of child-bearing potential/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 month 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. There are, however, no adequate and well-controlled studies in pregnant women and animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly justified. This medicine should not be used on pregnant women approaching term. Caution should be taken when it is administered to pregnant women.
Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/fetal development/ and-or/ parturition/ and-or/ postnatal development. SILVERDIN should not be used during pregnancy unless necessary.

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.

Fertility
There is not any data as to its effect on ability to conceive.

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, anemia due to deficiency of glucose-6-phosphate dehydrogenase, hemolytic anemia, poisoning by silver (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 important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: 0 800 314 00 08; fax: 0 312 218 35 99).

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 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
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 useful in situations where such agents are contraindicated.

5.2 Pharmacokinetic properties

General properties

Absorption:

There is evidence that in large area wounds and/or after prolonged application, systemic absorption of silver can occur causing clinical argyria. The sulfadiazine readily diffuses across wounds and enters the general circulation. The degree of uptake will significantly depend upon the nature of the wound and the dosing regimen.
Although silver is not appreciably 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 approach 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
36 months

6.4 Special precautions for storage
Store at room temperature below 30°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.

- *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

08016/09636/NMR/2022

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: Oct 28, 2022

10. DATE OF REVISION OF THE TEXT

16.11.2018