SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SILVERDIN PLUS 1% + 5% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g cream contains:
Active substances:
Silver sulfadiazine 10 mg
Lidocaine 50 mg

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

3. PHARMACEUTICAL FORM

White, odorless, soft consistency, water-miscible cream with homogeneous apperance.

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.
- For the prophylaxis and treatment of bacterial infections of the skin and dermal ulcers.

4.2 Posology and method of administration

To be applied topically. Not suitable for ocular administration.

Posology/frequency and duration of administration:
The dose of lidocaine applied at a time should not exceed 250 mg. This amount corresponds to 5 g of SILVERDIN PLUS. The daily dose of 17-20 g SILVERDIN PLUS (equivalent to 850-1000 mg lidocaine) should not be exceeded.
Very frequent application on a very large surface may cause hypersensitivity, therefore this kind of application is not recommended.

Method of administration:
In burns
SILVERDIN PLUS 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 PLUS cream should be re-applied at least every 24 hours, or more frequently if the volume of exudate is large.

Hand burns
SILVERDIN PLUS 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 PLUS cream to a depth of at least 3-5 mm. As SILVERDIN PLUS cream can cause maceration of normal skin on prolonged contact, care should be taken to prevent spread onto non-ulcerated areas.

Application of SILVERDIN PLUS 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 PLUS cream.

SILVERDIN PLUS 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 PLUS 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:
It should be used with caution in patients with severe renal or hepatic impairment. Silver sulfadiazine may accumulate in patients with impaired liver and kidney function.

Since lidocaine is metabolized in the liver, the half-life of lidocaine may be prolonged in patients with hepatic dysfunction. If liver failure occurs, treatment should be discontinued as it may cause hepatitis. In severe liver failure, only administration of the drug to smaller areas should be considered.

In case of renal failure with decreased renal elimination, treatment should be discontinued.

Pediatric population:
It should not be used in premature infants and newborns less than 2 months of age. The dose for children should be lower and appropriate for their age, weight and physical condition.

Systemic absorption of SILVERDIN PLUS may increase, when applied to large and damaged areas. This should be taken into consideration.

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, lidocaine, amide type anesthetics 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 PLUS 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 PLUS 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 PLUS is considered, it should be taken into consideration that the silver it contains may inactivate such enzymes.

SILVERDIN PLUS 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.

In cases of sepsis or if the mucosa where the medicine is to be applied is seriously damaged, there may be a risk of sudden systemic absorption. Care should be taken when applying SILVERDIN PLUS.

The lowest effective level where adequate effect is achieved should be used in order to prevent high plasma levels and serious side effects. Repeated doses may increase blood levels due to accumulation of the drug or its metabolites. Tolerance to high blood levels depends on the patient's condition. In the elderly, children and acute patients, a reduced dose should be given depending on the patient's age and physical condition.

SILVERDIN PLUS should be used with caution in patients with known drug allergies. There was no cross-sensitivity to lidocaine in patients with allergies to para aminobenzoic acid derivatives (such as procaine, tetracaine, benzocaine). When applied to large skin surfaces and especially under occlusion, it may lead to cardiac arrhythmias, difficulty breathing, coma and even death.

1 g SILVERDIN PLUS contains 40 mg cetyl alcohol. Cetyl alcohol may cause local skin reactions (such as contact dermatitis).
1 g SILVERDIN PLUS 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 PLUS 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. It is recommended to monitor blood levels of the hypoglycemic drug and phenytoin 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.

No drug interactions have been reported in the literature with local administration of lidocaine.

Additional information on special populations
There is no interaction study on specific populations.

Pediatric population
There is no interaction study on pediatric populations.

4.6 Fertility, 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 PLUS should not be used the last stage of pregnancy.

A reproductive study has been performed in rabbits at doses up to 3-10 times the concentration of silver sulfadiazine in SILVERDIN PLUS 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.

It should only be used when necessary in pregnant women. It should not be used during the last period of pregnancy.

Breastfeeding
It is unknown whether SILVERDIN PLUS 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
Although lidocaine has not been found to be harmful to rat and rabbit fetuses, the effect on the fetus of women is not known. Care is advised especially in early pregnancy.

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)

<u>Adverse effects with silver sulfadiazine use are:</u>

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

Adverse effects with lidocaine use are:
Side effects of lidocaine are similar to those of other amide-type local anesthetics. These side effects are generally dose-dependent and may occur as a result of high plasma concentrations due to high dose administration or rapid absorption. Serious side effects are usually systemic.

Immune system disorders
Uncommon: Allergic reactions (usually seen after parenteral treatment). Hypersensitivity may occur after long-term topical use.
Not known: Reactions due to decreased tolerance

Nervous system disorders
Not known: Irritability, dizziness, tremor, convulsions

Eye disorders
Not known: Vision disorders

Skin and subcutaneous tissue disorders

Common: Skin irritation, redness, itching or rash

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 via the national reporting system.

4.9 Overdose
Overdose is not expected with topical administration of silver sulfadiazine.

Overdose is not possible with topical use of lidocaine, but if it occurs, the airways should be kept open. Anticonvulsive agents may be used against convulsions. If a tube of drug is accidentally swallowed, oral bioavailability is low, but hypotension and heart block may occur. In this case, appropriate resuscitation measures should be applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Topically administered sulphonamide combinations
ATC code: D06BA51

Mechanism of action
Silver sulfadiazine has broad antimicrobial activity. It is bactericidal for many Gram negative and Gram positive bacteria as well as being effective against fungi. 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 useful in situations where such agents are contraindicated.

SILVERDIN PLUS cream contains lidocaine, a topical anesthetic. Lidocaine stabilizes neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. The effect starts within 3-5 minutes.

Elevated plasma levels of lidocaine cause changes in cardiac output, total peripheral resistance and mean blood pressure. These changes may be due to the blocking of autonomic nerve fibers with a direct depressant effect on various components of the cardiovascular system of the local anesthetic.

5.2 Pharmacokinetic properties

General properties

Silver sulfadiazine

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.

Lidocaine
Absorption:
Lidocaine is absorbed following topical administration to mucous membranes; its rate and extent of absorption being dependent upon the concentration and total dose administered, the specific site of application, and duration of exposure. Lidocaine is also well absorbed from the gastrointestinal tract, although little of the intact drug appears in the circulation because of biotransformation in the liver.

Distribution:
The plasma protein binding of lidocaine is dependent on the drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 microgram of free base per ml, 60 to 80 percent of lidocaine is protein-bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.
Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Metabolism:
Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Approximately 90% of lidocaine administered is excreted in the form of various metabolites.

Elimination:
Approximately 10% of lidocaine is excreted unchanged through the kidneys The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline. The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours.

Linearity/Non-linearity:
Not applicable.

Characteristic features in patients
Kidney/liver failure:
Since lidocaine is metabolized rapidly in the liver, the kinetics of lidocaine may be altered if liver function is affected.

Kidney failure does not affect lidocaine kinetics but may increase the accumulation of metabolites in the body.

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 PLUS was applied, indication of carcinogenicity was not found.

No sufficient studies have been conducted to evaluate the mutagenic and carcinogenic potential of lidocaine and its effects on fertility.

The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes in vitro, and by mouse micronucleus test *in vivo*. There was no indication in these tests of any mutagenic effects. The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatic exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/ml). No evidence of genotoxicity was found in the *in vivo* assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetyl alcohol
Glycerin monostereate
Liquid paraffin
Propylene glycol
Polysorbate 60
Polysorbate 80
Anhydrous citric acid
Sodium citrate dihydrate
Deionised water

6.2 Incompatibilities

SILVERDIN PLUS 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

50 g tube with a body of 92% LDPE, 8% LLDPE, a head of 100% LDPE and a cap of 100% PP, with a foiled mouth.

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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8. MARKETING AUTHORIZATION NUMBER(S)

255/77

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 31.12.2013
Date of last renewal :

10. DATE OF REVISION OF THE TEXT