1 NAME OF THE MEDICINAL PRODUCT

Bepanthen Plus.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: 1 g cream contains 50 mg dexpanthenol and 5 mg chlorhexidine dihydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antiseptic healing treatment of wounds of any kind with an infection risk, such as slight skin irritations, wounds, cuts, burns and skin inflammation.

4.2 Posology and method of administration

Apply a thin layer of cream on the affected area(s) up to 4 times daily.

The wound may either be left uncovered or bandaged.

Application to larger areas of skin should be avoided.

In the case of inflamed nipples during lactation: any cream adhering to the nipples should always be carefully and completely off before the baby is fed.

4.3 Contraindications

Bepanthen Plus must not be used in patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1. In addition, chlorhexidine must not be used on a perforated eardrum.
Bepanthen Plus is not to be used for wounds that are deep, serious or infected. Such wounds are to be treated by a doctor.

4.4 Special warnings and precautions for use

Avoid letting Bepanthen Plus come into contact with the eyes, ears or mucous membranes.

Bepanthen Plus should not be used for the treatment of irritated skin that is not specifically susceptible to infection (e.g. sunburn). Use of a medication without a disinfectant is recommended for this purpose.

If symptoms do not improve after 10 – 14 days or get worse, patients should be told to contact a doctor. Prescribing doctors should inform their patients about early and mild/moderate symptoms of an allergic reaction with the corresponding clinical manifestations, including mild to moderate reactions of the skin (e.g. pruritus, urticaria), the face (e.g. angioedema), the respiratory tract (e.g. asthma, wheezing or other breathing problems), the gastrointestinal tract and the cardiovascular system and, where this is the case, instruct them to stop using Bepanthen Plus immediately and contact their doctor, as this can mitigate or even prevent progression to a life-threatening reaction.

Bepanthen Plus cream contains wool wax (lanolin), cetyl alcohol and stearyl alcohol. These may cause localised skin irritation (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Due to possible interference (antagonism/inactivation), the concurrent use of Bepanthen Plus and other antiseptics should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no clinical data on use in pregnant women.
Reproduction studies in animals have shown no risks to foetuses, but no controlled studies in pregnant women are available. Nevertheless, application over large areas should be avoided during pregnancy.

Lactation:
Bepanthen Plus may be used during lactation, but not over large areas. Cream residues must be removed before breastfeeding, to ensure that they are not ingested by the infant.

4.7 Effects on ability to drive and use machines

Bepanthen Plus is not known to have any negative effects on the ability to drive or use machines.

4.8 Undesirable effects

The undesirable effects listed are based on spontaneous reports, which is why CIOMS III categorisation is not possible.

Immune system disorders, skin and subcutaneous tissue disorders, hypersensitivity reactions, anaphylactic reactions ranging up to anaphylactic shock to the Bepanthen Plus ingredient chlorhexidine, with the corresponding clinical manifestations including mild to moderate reactions of the skin (e.g. pruritus, urticaria), the face (e.g. angioedema), the respiratory tract (e.g. asthma, wheezing or other breathing problems), the gastrointestinal tract and the cardiovascular system have been observed.

Reporting suspected adverse reactions
The reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulations by using an online form at:
https://sideeffects.health.gov.il/

4.9 Overdose

Dexpanthenol is also well tolerated in high doses and is therefore classified as safe. Hypervitaminosis is not known. Aminotransferase elevation has been reported following intoxication with self-administered oral chlorhexidine.

Repeated topical use on the same area can lead to skin irritation. The product is suitable for smaller skin lesions only. Application to large areas must be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: D08AC52

Mechanism of Action/pharmacodynamics effects/clinical efficacy

Dexpanthenol is rapidly converted in cells into pantothenic acid which, as a component of the essential coenzyme A, plays a key role in the metabolism of every cell. Pantothenic acid is essential to the construction of the epithelium of skin and mucous membranes.

During wound healing, the mitosis rate and the tear resistance of collagen fibres increase. Chlorhexidine dihydrochloride is a known and well-tolerated antiseptic with bactericidal activity against Gram-positive bacteria, e.g. sensitive strains of Staphylococcus aureus, which are the most common causative agents of skin infections. To a slightly lesser degree, it is also effective against Gram-negative microbes. Some species of Pseudomonas and Proteus are resistant. It is only weakly active against fungi and is ineffective against viruses.

Pharmacodynamics
No studies have been carried out.

Clinical efficacy
No data available

5.2 Pharmacokinetic properties

Absorption
Dexpanthenol is absorbed quickly by the skin, converted immediately into the vitamin pantothenic acid and added to the endogenous pantothenic acid pool.

There are no indications of chlorhexidine absorption through unbroken skin in adults. When infants were bathed in a 4% chlorhexidine gluconate detergent solution, chlorhexidine was detected at low concentrations (≤1 µg/ml) in the blood.

Distribution
In the blood, pantothenic acid is bound to plasma proteins (in particular beta-globulin and albumin). In healthy adults, approximately 500 – 1000 µg/L is found in whole blood and approximately 100 µg/L in the serum.

Due to low percutaneous absorption, there are few reliable facts concerning the distribution of chlorhexidine in organs and tissue. After oral administration (300 mg), maximum plasma levels of approx. 0.2 µg/mL are reached after 30 minutes in healthy adults.

Metabolism
Pantothenic acid is not broken down in the body but is excreted unchanged.

Elimination
60 – 70% of an oral dose of pantothenic acid is excreted in the urine and the rest in the faeces. Adults excrete around 2 – 7 mg per day in urine and children 2 – 3 mg.

Topically applied chlorhexidine is not absorbed percutaneously. Following oral administration, chlorhexidine is eliminated almost completely in the faeces.

Kinetics in specific patient groups:
No studies have been carried out.

5.3 Preclinical safety data

Acute toxicity
Pantothenic acid and its derivatives are considered non-toxic. Following the oral administration of dexpanthenol in mice and of chlorhexidine salts in mice/rats, the LD_{50} values were 15 g/kg and >2 g/kg, respectively.

Long-term toxicity (also known as repeated-dose toxicity)
A daily oral intake of dexpanthenol in rats (200 mg/kg) and dogs (500 mg/kg) over a period of 3 months showed no toxic effects or histological changes.

Skin toxicity
Studies with the combination of panthenol and chlorhexidine in rabbits and guinea pigs showed no irritant effects on the skin.

Mutagenicity

Studies on the mutagenic potential of chlorhexidine and pantothenic acid provided no indications of any clinically relevant effects.

Reproductive toxicity
No embryonic or foetal malformations and no impairment of fertility were observed following the oral administration of chlorhexidine to pregnant rats.
The combined oral administration of pantothenic acid and chlorhexidine had no negative effect on fertility or development in dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin, white soft paraffin, cetyl alcohol, macrogol stearate, wool fat, stearyl alcohol, DL-Pantolactone, purified water.

6.2 Incompatibilities

Chlorhexidine is incompatible with soap and other anionic substances.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening, use within 12 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

The off-white cream is filled into aluminium tubes with screw-on caps and enclosed in an outer carton. Registered Pack sizes are 3.5g, 30g and 100g. Not all pack sizes may be marketed.

6.6 Manufacturer

GP Grenzach Produktions GmbH, Germany

6.7 Registration number in Israeli National Drug Registry:

127-48-26501-01

6.8 MARKETING AUTHORISATION HOLDER

Bayer Israel Ltd., 36 Hacharash St., Hod HaSharon, 45240

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