Data Sheet

NERISONE®

Diflucortolone valerate-containing topical preparations.

Presentation

Nerisone® Cream:

1 g white cream contains 1 mg (0.1 %) diflucortolone valerate. The cream is an oil in water emulsion containing approximately 70% water.

Nerisone® Ointment:

1 g white to yellowish white ointment contains 1 mg (0.1 %) diflucortolone valerate. The cream is a water in oil emulsion with a water content of 30%.

Nerisone® Fatty Ointment:

1 g white single-phase fatty ointment contains 1 mg (0.1 %) diflucortolone valerate.

Uses

Actions

NERISONE® suppresses inflammation in inflammatory and allergic skin conditions and alleviates subjective complaints such as itching, burning and pain.

Capillary dilatation, intercellular oedema and tissue infiltration regress; capillary proliferation is suppressed. This leads to fading of inflamed skin surfaces.

Pharmacokinetics

The NERISONE® product line contains as its active ingredient diflucortolone valerate, the 21- monoester of diflucortolone with valeric acid, in a concentration of 0.1 %.

So that the Nerisone® formulations are able to exert their therapeutic antiproliferative and antiinflammatory effects in the skin, it is necessary for

diflucortolone valerate to diffuse from the respective formulations into the living epidermis or upper corium. In-vitro penetration studies have shown that diflucortolone valerate quickly penetrates human skin from all galenic formulations.

The following highest substance levels were found in the horny layer 4 hours after application: approx. 300 mcg/ml (around 600 micromol/ml) after treatment with fatty ointment and ointment, and approx. 500 mcg/ml (around 1000 micromol/ml) after application of the cream. The corticoid concentration falls in the horny layer from distally to proximally by around 1.5 - 2 powers of 10. After application to damaged skin - as the model for diseased skin -, the local corticoid concentrations in the living skin were far higher at all time points studied than after application to intact skin.

Diflucortolone valerate is partially hydrolysed to diflucortolone while still in the skin. Diflucortolone binds even stronger to the corticoid receptor than the parent drug. Some of the corticosteroid applied to the skin is absorbed percutaneously and distributed in the organism; it then undergoes further metabolic breakdown before being eliminated.

The degree of percutaneous absorption and the resulting systemic load depend on a number of factors such as the nature of the vehicle, the exposure conditions (skin area dose, size of the treated area, duration of treatment), the nature of the treatment (open/occlusive), the condition of the skin barrier and the area of the body to be treated.

After simultaneous dermal application of the radioactively labelled cream, ointment and fatty ointment to different fields of skin on the backs of 6 volunteers with healthy skin, the amounts of the applied dose absorbed within a mean period of exposure of 4 hours were approx. 0.2 % via intact skin and approx. 0.4 % via "stripped" skin. Extrapolated to a whole day, this results in a mean percutaneous absorption of approx. 1.2 % in the case of an intact penetration barrier and of approx. 2.4 % in the case of a removed barrier.

Following absorption, diflucortolone valerate is hydrolysed extremely quickly to diflucortolone and the corresponding fatty acid. In addition to diflucortolone, 11-keto-diflucortolone and two other metabolites were recovered in plasma. Diflucortolone is eliminated from plasma with a half-life of around 4 - 5 hours, all metabolites with a half-life of around 9 hours (half-lives were determined after i.v. administration), and excreted with urine and faeces in the proportion 75 : 25.

Indications

All skin diseases which respond to topical corticoid therapy (eg): contact dermatitis, contact eczema, occupational eczema vulgar, nummular, degenerative and seborrhoeic eczema, dyshidrotic eczema, eczema in varicose syndrome (but not directly onto lower limb ulcers), anal eczema, eczema in

children, neurodermatitis (endogenous eczema, atopic dermatitis), psoriasis, lichen ruber planus et verrucosus, lupus erythematosus discoides first degree burns, sunburn, insect bites.

Dosage and Administration

At the beginning of treatment, the NERISONE® preparation best suited to the skin condition is applied thinly twice or, perhaps, three times per day. Once the clinical picture has improved, one application per day usually suffices.

Babies and children up to the age of 4 years should not be treated with NERISONE® for longer than three weeks, particularly on skin areas covered by nappies.

NERISONE® is available in cream, ointment and fatty ointment. Which form should be used in the individual case will depend on the appearance of the skin: NERISONE® CREAM in weeping skin conditions, NERISONE® OINTMENT in skin conditions which are neither weeping nor very dry, and NERISONE® FATTY OINTMENT in very dry skin conditions.

- NERISONE® CREAM has a high water and low fat content. In weeping skin diseases it allows secretions to drain away, thus providing for rapid subsidence and drying up of the skin. It is also suitable for application to moist, exposed and hairy areas of the body.

If the skin dries out too much under protracted use of NERISONE® CREAM, the patient should be switched to a form which contains more fat (NERISONE® OINTMENT OR NERISONE® FATTY OINTMENT).

- NERISONE® OINTMENT

Skin conditions which are neither weeping nor very dry require a base with balanced proportions of fat and water. NERISONE® OINTMENT makes the skin slightly greasy without retaining heat or fluid. Of the three different forms of NERISONE®, the ointment has the widest range of use.

- NERISONE® FATTY OINTMENT

Very dry conditions and chronic stages demand an anhydrous fatty base. The occlusive effect of the NERISONE® FATTY OINTMENT base promotes the healing process.

Occlusive dressings

An occlusive dressing may be called for in unusually refractory cases. When it is, it should be as follows managed : After application of the appropriate NERISONE® preparation, the area under treatment should be covered with a

plastic foil which should then be fixed firmly all round to healthy skin by means of adhesive plaster. Plastic gloves can be used to occlude the hands.

The dressing should be kept in place for as long as can be expected of the patient, but generally not for longer than 24 hours. If the occlusive treatment is expected to be prolonged, it is advisable to change the dressing every 12 hours.

If an infection develops under the dressing, occlusive treatment must be terminated.

Contraindications

Tuberculous or syphilitic processes in the area to be treated; virus diseases (e.g. vaccinia, chickenpox, shingles).

Warnings and Precautions

Preclinical safety data

In systemic tolerance studies following repeated dermal and subcutaneous administration the effect of diflucortolone valerate was that of a typical glucocorticoid. It can be derived from these results that no side effects further to those which are typical of glucocorticoids are to be expected following therapeutic use of NERISONE® preparations under extreme conditions such as application over large areas and/or occlusion.

Specific embryotoxicity studies with diflucortolone valerate following subcutaneous and dermal administration led to results typical of glucocorticoids, i.e. following sufficiently high exposure embryolethal and/or teratogenic effects could be induced given the appropriate test systems.

Since epidemiological studies have as yet given no indications of embryotoxic effects due to systemic glucocorticoid therapy, no embryotoxic effects are to be expected following the therapeutic use of NERISONE® preparations. However, taking animal-experimental results into consideration, particular care should be taken when prescribing NERISONE®.

In vitro investigations for detection of gene mutations in bacteria and mammalian cells as well as in vitro and in vivo examinations for detection of chromosome and gene mutations have not given any indications of a mutagenic potential of diflucortolone valerate.

Specific tumorigenicity studies have not been carried out with diflucortolone valerate. On the basis of the pharmacodynamic action pattern, the lack of

evidence of a genotoxic potential, the structural properties and the results of chronic toxicity tests (no indication of proliferative changes), there is no suspicion of a tumorigenic potential of diflucortolone valerate. Since systemically effective immunosuppressive dosages will not be reached after dermal application of NERISONE® if used as directed, no influence on the occurrence of tumours is to be expected.

According to the results from local tolerance studies following repeated dermal administration, no dermal changes further to the side-effects already known for topical preparations containing glucocorticoids are to be expected from therapy with NERISONE®.

Pregnancy and Lactation

As a general rule, topical preparations containing corticoids should not be applied during the first trimester of pregnancy. In particular, application to large areas of the body or for prolonged periods must be avoided.

Adverse Effects

The following reactions may occur when NERISONE® is applied to large areas of the body (about 10 % and more) and/or for long periods of time (more than 4 weeks): particularly when the fatty ointment or an occlusive dressing is used: local concomitant symptoms such as atrophy of the skin, telangiectasia, striae, acneform changes of the skin, perioral dermatitis, increased growth of body hair (hypertrichosis) and systemic effects of the corticoid due to absorption. In rare cases allergic skin reactions may occur.

Side effects cannot be excluded in neonates whose mothers have been treated extensively or for a prolonged period of time during pregnancy or while lactating (for example, reduced adrenocortical function, when applied during the last weeks of pregnancy).

Interactions

None so far known.

Overdosage

On the basis of results from acute toxicity studies with both diflucortolone valerate and the NERISONE® preparations no acute risk of intoxication is to be expected either after a single dermal application of an overdose (application over

a large area under conditions favouring resorption) or even after inadvertent oral intake of a whole package.

Pharmaceutical Precautions

Shelf life: Cream - 3 years, Ointment and Fatty Ointment - 5 years.

Special precautions for storage

Cream: Store below 25 °C.

Ointment, Fatty Ointment: Store below. 25 °C

Medicine Classification

Prescription Medicine

Package Quantities

Tubes made of pure aluminium, interior wall coated with epoxy resin, and with a polyester-based external coating, fold seal ring is made of polyamide based heat sealable material. The screw cap is made of high density polyethylene.

Further Information

List of excipients

Cream: White soft paraffin, liquid paraffin, stearyl-alcohol, poly-oxyl 40 stearate, polyacrylic acid (Carbopol 934), sodium hydroxide disodium edetate dihydrate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, purified water.

Ointment: White soft paraffin, liquid paraffin, Dehymuls E, white bees wax, purified water.

Fatty Ointment: White soft paraffin, liquid paraffin, microcrystalline wax, hydrogenated castor oil.

Instructions for use/handling

Store all drugs properly and keep them out of reach of children.

Name and Address

Sponsor

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