REGISTERED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ADVANTAN MILK

Corticoid skin preparations

COMPOSITION

1 g Advantan contains methylprednisolone aceponate (21-acetoxy-11β-hydroxy-6α-methyl-17-propionyloxy-1,4-pregnadiene-3,20-dione) 1 mg.
The milk contains benzyl alcohol 1,25% (w/w) as preservative.

PHARMACOLOGICAL CLASSIFICATION

A. 13.4.1 Corticosteroids without anti-infective agents.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

After topical application, Advantan Milk suppresses inflammatory and allergic skin reactions as well as reactions associated with hyperproliferation, leading to regression of the objective symptoms (erythema, oedema, weeping) and the subjective complaints (itching, burning, pain).

The mechanism of action of methylprednisolone aceponate is not completely understood. It is known that methylprednisolone aceponate itself binds to the intracellular glucocorticoid receptor and this is especially true for the principal metabolite methylprednisolone-17-propionate, which is formed after cleavage in the skin.

The steroid receptor complex binds to certain regions of DNA, thereby triggering a series of biological effects.

The understanding of the mechanism of the anti-inflammatory action is more precise. Binding of the steroid receptor complex results in induction of macrocortin synthesis. Macrocortin inhibits the release of arachidonic acid and thus the formation of inflammatory mediators such as prostaglandins and leukotrienes.

The immunosuppresive action of glucocorticoids can be explained by inhibition of cytokine synthesis and an antimitotic effect, which so far is not well understood.

Inhibition of the synthesis of vasodilating prostaglandins or potentiation of the vasoconstrictive effect of adrenalin finally results in the vasoconstrictive activity of glucocorticosteroids.

Pharmacokinetic properties

Methylprednisolone aceponate becomes available in the skin after application of the Advantan formulations. The concentration in the stratum corneum and living skin decreases from the outside to the inside.

Methylprednisolone aceponate is hydrolised in the epidermis and dermis to the main metabolite methylprednisolone-17-propionate which binds more firmly to the corticoid receptor than the parent drug.

The rate and extent of percutaneous absorption of a topical corticosteroid depends on a series of factors: chemical structure of the compound, the composition of the vehicle, the concentration of the compound in the vehicle, the conditions of exposure (area dose, duration of exposure, open or occlusion) and the skin status (kind and severity of skin disease, anatomical site, etc).

For investigating the percutaneous absorption of methylprednisolone aceponate from the milk formulation, the status of the skin was artificially changed. Intact skin was compared with artificially inflamed (UV-B-erythema) and artificially damaged skin (removal of horny layer). The extent of absorption through artificially inflamed skin was very low (0,27% of the dose) and was only marginally higher than the absorption through intact skin (0,17% of the dose). The percutaneous absorption of methylprednisolone aceponate through skin pre-damaged by stripping, resulted in distinctly higher values (15% of the dose). Based on these figures the systemic corticosteroid load after whole body treatment could amount to approximately 4 μg methylprednisolone aceponate-equivalents per kg body weight and day, which would exclude systemic corticosteroid effects.

After reaching the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, methylprednisolone-17-propionate is quickly conjugated with glucuronic acid and as a result, inactivated.

The metabolites of methylprednisolone aceponate (main metabolite: methylprednisolone-17-propionate-21-glucuronide) are eliminated primarily via the kidneys with a half-life of about 16 hours. Following intravenous administration, excretion with the urine and faeces was complete within 7 days. No retention of drug substance or metabolites takes place in the body.

INDICATIONS

Treatment of acute exogenous (allergic contact dermatitis, toxic degenerative eczema, seborrhoeic eczema, nummular (microbial) eczema, dyshidrotic eczema, gravitational eczema, unclassifiable eczema) and endogenous eczema (atopic dermatitis, neurodermatitis).

CONTRA-INDICATIONS

Presence of tuberculous or syphilitic processes, chickenpox, zoster and other viral infections, rosacea, perioral dermatitis and postvaccination skin reactions in the area to be treated.

Corticosteroids have been shown to be teratogenic in animals following dermal application. As these agents are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore Advantan should not be used during pregnancy.

DOSAGE AND DIRECTIONS FOR USE

For external use only.

Advantan Milk is to be used only as necessary and applied thinly once daily to the affected areas and rubbed in lightly.

In general, the duration of use should not exceed 2 weeks.

If the skin dries out excessively under use of the Advantan Milk a switch should be made to one of the formulations with a higher fat content (Advantan ointment or fatty ointment).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Occasionally, Advantan Milk may lead to local skin irritations such as a mild transient burning sensation.

Less frequently, itching, erythema, dry skin, scaling and folliculitis may arise.

Hypersensitivity reactions to the components may occur.

Long-term continuous treatment with topical corticosteroids should be avoided as far as possible as this may cause atrophic changes in the skin leading to thinning, loss of elasticity, dilatation of superficial blood vessels, telangiectasiae and ecchymoses. These changes are particularly likely to occur on the face and when occlusive dressings are used.

Systemic absorption of topically applied corticosteroids may occur, particularly under the following conditions: when large quantities are used, or when application is made to wide areas of the body, or to damaged skin, when potent topical corticosteroids are used, and when the occlusive dressing technique is applied. Depression of the hypothalamic-pituitary-adrenal axis with consequent suppression of the adrenal gland may occur. These effects are most likely to be severe in children. Growth may be retarded and a Cushingoid state may be produced. Benign increased intracranial pressure has been rarely reported.

No impairment of the adrenocortical function has been observed in adults on large area treatment (40 to 60% of the skin surface) even under occlusive conditions with Advantan. Nevertheless, the duration of use should be as brief as possible if large areas have to be treated.

Additional, specific therapy is required in bacterially infected skin diseases and/or in fungus infections.

Care must be taken when using Advantan Milk to avoid contact with the eyes.

The clinical indication for treatment with Advantan Milk must be very carefully reviewed and the benefits weighed against the risks in lactating women. In particular, large area treatment should be avoided. Nursing mothers should not be treated on the breasts.

Topical corticosteroids should be used with particular caution in facial dermatoses, and only for short periods. A steroid rosacea-like facies may be produced.

Regular review should be made of the necessity for continuing therapy.

This corticosteroid preparation should not be used in the nappy areas in infants for flexural eruptions, and ideally it should not be applied to infants and young children.

The treatment of psoriasis with potent topical corticosteroids may provoke the pustular form of the disease.

Advantan should not be applied to skin crease areas.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Please refer to the paragraph "Side-effects and special precautions". If any symptoms of overdosage occur, treatment must be discontinued.

IDENTIFICATION

White, opaque emulsion.

PRESENTATION

Tubes of 20 g or 50 g.

STORAGE INSTRUCTIONS

Store below 30°C. Keep well closed. Keep out of reach of children.

REGISTRATION NUMBER

32/13.4.1/0362

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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