PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Advantan Cream 0,1 % w/w

Advantan Fatty Ointment 0,1 % w/w

Advantan Ointment 0,1 % w/w

Corticoid skin preparations

2. QUALITATIVE AND QUANTATIVE COMPOSTION

1g Advantan contains methylprednisolone aceponate (21-acetoxy-11β-hydroxy-6α-methyl-17-propionyloxy-1,4-pregnadiene-3,20-dione) 1 mg.

Excipients with known effect: The cream contains benzyl alcohol, butyl hydroxytoluene and cetylstearyl alcohol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream : White opaque cream.

Fatty ointment : White to yellowish translucent fatty ointment.

Ointment : White to yellowish-white opaque ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endogenous eczema (atopic dermatitis, neurodermatitis), contact eczema, dyshidrotic and other eczemas.

4.2 Posology and method of administration

Posology

The Advantan formulation appropriate to the skin condition is applied thinly once per day to the diseased areas of skin.

In general, the duration of use should not exceed 12 weeks in adults and 4 weeks in children.

The respective bases are of major importance to the therapeutic effect of the Advantan formulations.

Advantan Cream

As a low-fat formulation with a high-water content, Advantan cream is particularly suitable for acute and weeping stages of eczema, for very greasy skin and for use on exposed or hairy parts of the body.

If the skin dries out excessively under protracted use of Advantan cream, a switch should be made to one of the fattier formulations (Advantan ointment or fatty ointment).

Advantan Fatty Ointment

Very dry skin conditions and chronic stages of skin diseases require an anhydrous base. The occlusive effect of the fatty ointment base promotes the healing procedure.

Advantan Ointment

Skin conditions which are neither weeping nor very dry require a base with balanced proportions of fat and water. Advantan ointment makes the skin slightly greasy without retaining warmth and fluid. Of the three formulations, Advantan ointment has the widest field of use.

Method of administration

For external use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Tuberculous or syphilitic processes in the area to be treated; virus diseases (e.g., herpes simplex, vaccinia, chickenpox, shingles).
- Primary bacterial, viral and fungal diseases of the skin and secondarily infected eczemas or intertrigo acne, perioral dermatitis, rosacea atrophic skin diseases and vaccination skin reactions in the area to be treated and, in general, should not be used on weeping surfaces.
- Corticosteroids have been shown to be teratogenic in animals following dermal application. As these medicines are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore, Advantan should not be used during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Advantan should be used at the lowest possible dose, particularly among children, and only for the time strictly necessary to achieve and maintain the desired therapeutic effect.

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, telangiectasia and ecchymoses. These changes are particularly likely to occur on the face and when occlusive dressings are used.

If a secondary microbial skin infection is present suitable concomitant antimicrobial therapy should be instituted. If fungal infections are present, a topically active antimycotic should be applied. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate therapy.

Local skin infections can be exacerbated by topical glucocorticoid use.

Care must be taken when using Advantan to avoid contact with the eyes, deep open wounds and mucosae. Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

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 adrenocortical function has been observed in children on large-area (40 - 90 % of the skin surface) non-occlusive treatment with Advantan 0,1 % fatty ointment. After application of Advantan 0,1 % ointment to 60 % skin surface area under occlusive conditions for 22 hours, suppression of plasma cortisol levels and influence on circadian rhythm was observed in adult healthy volunteers.
Extensive application of topical corticosteroids to large areas of the body or for prolonged periods of time, in particular under occlusion, significantly increases the risk of side effects. Treatment under occlusive conditions should be avoided unless indicated. Note that diapers/nappies as well as intertriginous areas might represent occlusive conditions.

When treating large areas of skin, the duration of treatment should be kept as short as possible as the possibility of absorption or a systemic effect cannot be completely excluded.

Unprofessional use of Advantan can mask clinical symptomatology.

Glaucoma may also develop from using local corticoids, like Advantan (e.g., after large-dosed or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin

around the eyes).

Acneiform skin conditions can occur under therapy with potent corticoids. Topical corticosteroids should be used with particular caution in facial dermatoses, and only for short periods. Steroid rosacea-like facies may be produced. If rosacea or perioral dermatitis is present, Advantan must not be applied to the face.

Advantan should be used with caution during breastfeeding with regular review of the necessity for continuing with treatment (see section 4.6).

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.

Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

Advantan cream contains butyl hydroxytoluene which may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes, and cetylstearyl alcohol which may cause local skin reactions (e.g., contact dermatitis).

The excipient (hard fat) in Advantan cream may reduce the effectiveness of latex products such as condoms and diaphragms.

Advantan cream also contains 1,0 g benzyl alcohol in each 100 g. Benzyl alcohol may cause allergic reactions and/or mild local irritation.

Paediatric Population

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.

4.5 Interaction with other medicinal products and other forms of interactions

None so far known.

Paediatric population

No information available.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Advantan cream, ointment and fatty ointment in pregnant women.

Animal experimental studies with glucocorticosteroids have shown reproductive toxicity (see section 5.3). A number of epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with systemic glucocorticosteroids during the first trimester of pregnancy.

Breastfeeding

In rats, methylprednisolone aceponate showed practically no transfer to the neonates via the milk. But it is not known if methylprednisolone aceponate is secreted in human milk as systemically administered corticosteroids have been reported to appear in human milk. It is not known whether topical

administration of Advantan cream, ointment and fatty ointment could result in sufficient systemic absorption of methylprednisolone aceponate to produce detectable quantities in human milk.

Therefore, caution should be exercised when Advantan cream, ointment and fatty ointment are used by breastfeeding women.

Breastfeeding women should not apply Advantan to the breasts. During breastfeeding, the treatment of extensive areas, prolonged use and occlusive dressings should be avoided (see section 4.4).

Fertility

There is no information available on the effect of methylprednisolone aceponate on fertility.

4.7 Effects on ability to drive and use machines

Blurred vision has been reported on patients using Advantan. The frequency of this adverse reaction is unknown (see section 4.8). Patients should be warned that Advantan may impair their ability to drive and use machines.

4.8 undesirable effects

a. *Summary of the safety profile*

In clinical studies, most frequently observed side-effects included application site burning and application site pruritus with Advantan cream and Advantan ointment. For Advantan fatty ointment, application site folliculitis and application site burning were observed most frequently.

b Tabulated list of adverse reactions

Frequencies of side-effects observed in clinical studies and given in the table below are defined according to the MedDRA frequency convention: 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 available data). MedDRA version 12.0 was used for coding.

Advantan cream

MedDRA System Organ Class	Description and frequency
General disorders and administration site reaction	*Common*: application site itching, burning, application site pruritus *Uncommon*: application site dryness, application site erythema, application site vesicles, application site folliculitis, application site rash, application site paraesthesia *Rare*: application site cellulitis, application site edema, application site irritation *Frequency not known*: hypertrichosis
Immune system disorders	*Uncommon*: drug hypersensitivity
Infections and infestations	*Rare*: fungal skin infection
Skin and subcutaneous tissue disorders	*Rare*: pyoderma, skin fissures, telangiectasia, skin atrophy, acne *Frequency not known**: skin striae, perioral dermatitis, skin discolouration, allergic skin reaction, withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules**
Eye disorders	*Frequency not known**: Blurred vision**

Advantan Fatty ointment

MedDRA System Organ Class	Description and frequency
General disorders and administration site reaction	*Common*: application site itching, burning, application site folliculitis

	Uncommon: application site pustules, application site erythema, application site vesicles, application site pain, application site pruritus, application site papules *Frequency not known*: hypertrichosis
Immune system disorders	*Uncommon*: drug hypersensitivity
Skin and subcutaneous tissue disorders	*Uncommon*: skin fissures, telangiectasia, *Frequency not known**: Acne, skin atrophy, skin striae, perioral dermatitis, skin discolouration, allergic skin reaction, withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules**
Eye disorders	*Frequency not known**: Blurred vision**

Advantan ointment

MedDRA System Organ Class	**Description and frequency**
General disorders and administration site reaction	*Common*: itching, burning, folliculitis, *Uncommon*: pustules, blisters, pruritus, pain, erythema, papules *Frequency not known*: hypertrichosis
Immune system disorders	*Uncommon*: drug hypersensitivity
Skin and subcutaneous tissue disorders	*Rare*: skin fissures, telangiectasia, *Frequency not known*: skin atrophy, acne, skin striae, perioral dermatitis, skin discolouration, allergic skin reaction, withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules**

Eye disorders	*Frequency not known**: Blurred vision**

* Potential undesirable effects not observed in clinical trials.

** See also section 4.4

The most appropriate MedDRA term (MedDRA version 11.1) was used to describe a certain adverse reaction, its symptoms and related conditions.

c. Description of selected adverse reactions

Systemic effects due to absorption may occur when topical preparations containing corticosteroids are applied.

As with other corticoids for topical application, the following local side effects may occur: skin atrophy, skin striae, application site folliculitis, hypertrichosis, telangiectasia, perioral dermatitis, skin discolouration and allergic skin reactions to one of the ingredients of the formulations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 Additionally, suspected adverse reactions can be reported to the Holder of Certificate of Registration via Adcock.AEReports@adcock.com.

4.9 Overdose

Please refer to the paragraph in section 4.4. If any symptoms of overdosage occur, treatment must be discontinued.

Results from acute toxicity studies do not indicate that any risk of acute intoxication is to be expected

following a single dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION

A. 13.4.1 Corticosteroids without anti-infective agents.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: corticosteroids, potent (group III), ATC code: D07AC14

PHARMACOLOGICAL ACTION

After topical application, Advantan has anti-inflammatory, anti-pruritic and vasoconstrictive actions. It suppresses Allergic skin reactions as well as reactions associated with hyperproliferation, leading to regression of the objective symptoms (erythema, oedema, infiltration, lichenification) and the subjective complaints (itching, burning, pain).

It is known that methylprednisolone aceponate itself binds to the intracellular glucocorticoid receptor and this is especially true of the principal metabolite 6 alpha-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.

Binding of the steroid receptor complex results in induction of macrocortin synthesis. Macrocortin inhibits the release of arachidonic acid and thus the formation of inflammation mediators such as prostaglandins and leukotrienes.

The immunosuppressive 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 adrenaline finally result in the vasoconstrictive activity of glucocorticoids.

5.2 Pharmacokinetic properties

Methylprednisolone aceponate becomes available in the skin from the formulation base. The concentration in the stratum corneum and living skin decreases from outside to inside.

Methylprednisolone aceponate is hydrolysed in the epidermis and dermis to the main metabolite 6 alpha-methylprednisolone-17-propionate which binds more firmly to the corticoid receptor than the parent drug, an indication of bioactivation in the skin.

The rate and extent of percutaneous absorption of a topical corticoid 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 treated, duration of exposure, open or occlusion) and the skin status (kind and severity of skin disease, anatomical site etc.).

Percutaneous absorption of methylprednisolone aceponate from the cream, ointment and fatty ointment formulations has been investigated in healthy volunteers. The percutaneous absorption after open application of the Advantan fatty ointment (2 x 20 g daily) for 5 days was estimated to 0,34 % corresponding to a corticoid load of approximately 2 µg/kg/day. The respective figures after open application of the Advantan ointment (2 x 20 g daily) for 8 days were 0,65 % (absorption) or 4 µg/kg/day (load). Under occlusive conditions the daily application of 2 x 20 g Advantan cream for 8 days led to a mean percutaneous absorption of ca. 3 % corresponding to a systemic corticoid load of ca. 20 µg/kg/day. The percutaneous absorption of methylprednisolone aceponate through skin pre-damaged by removal of the stratum corneum resulted in distinctly higher absorption (13-27 % of the dose). In adult psoriatic and atopic patients, percutaneous absorption of methylprednisolone aceponate from the fatty ointment was about 2,5 %. In three atopic children (9-10 years of age), percutaneous absorption of methylprednisolone aceponate from the fatty ointment was about 0,5-2 % and thus not higher than that compared to adults.

After reaching the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, 6 alpha-methylprednisolone-17-propionate, is quickly conjugated with glucuronic acid and inactivated as a result.

The metabolites of methylprednisolone aceponate (main metabolite: 6 alpha-methylprednisolone-17-propionate-21-glucuronide) are eliminated primarily via the kidneys with a half-life of about 16 hours. Following i.v. administration, excretion of the ^{14}C-labelled substances with the urine and faeces was completed within 7 days. No accumulation of substance or metabolites takes place in the body.

5.3 Preclinical safety data

In systemic tolerance studies following repeated subcutaneous and dermal administration methylprednisolone aceponate showed the action profile of a typical glucocorticoid. It can be concluded from these results that following therapeutic use of Advantan cream, ointment and fatty ointment no side-effects other than those typical of glucocorticoids are to be
expected even under extreme conditions such as application over a large surface and/or
occlusion.
Embryotoxicity studies with Advantan led to results typical for glucocorticoids, i.e., embryolethal and/or teratogenic effects are induced in the appropriate test system.

In view of these findings, particular care should be taken when prescribing Advantan during pregnancy. The results of epidemiological studies are summarized under section
"4.6 Pregnancy and lactation".

Neither *in vitro* investigations for detection of gene mutations on bacteria and mammalian cells nor *in vitro* and *in vivo* investigations for detection of chromosome and gene mutations gave any indication of a genotoxic potential of methylprednisolone aceponate.
Specific tumorigenicity studies using methylprednisolone aceponate have not been carried out.

Knowledge concerning the structure, the pharmacological effect mechanism and the results from systemic tolerance studies with long-term administration do not indicate any increase in the risk of tumor occurrence. As systemically effective immunosuppressive exposure is not reached with dermal application of Advantan cream, ointment and fatty

ointment under the recommended conditions of use, no influence on the occurrence of tumors is to be expected.

In investigations of local tolerance of methylprednisolone aceponate and Advantan formulations on the skin and the mucosa, no findings other than the topical side effects known for glucocorticoids were recorded.

Methylprednisolone aceponate showed no sensitising potential on the skin of a guinea-pig.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Advantan Cream

Benzyl alcohol

Butyl hydroxytoluene

Caprylic-capric-myristic-stearic triglyceride (Softisan 378)

Cetostearyl alcohol

Decyl oleate

Disodium edetate

Glycerol 85 per cent

Glycerol monostearate 40-55

Hard fat

Macrogol stearate 40, type I (Polyoxyl-40-stearate)

Water purified

Advantan Fatty Ointment

Hydrogenated castor oil

White soft paraffin

Paraffin liquid

Microcrystalline wax

Advantan Ointment

Beeswax white

Dicocoyl pentaerythrityl distearyl citrate + sorbitan sesquioleate + beeswax + aluminum stearates (Dehymuls E)

Paraffin liquid

Paraffin white soft

Water purified

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Advantan Cream and Ointment: 2 Years

Advantan Fatty Ointment: 5 Years

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Tubes of 15, 20, 30, 50 or 100 g.

Aluminium tube with screw cap polyethylene white (4669) packaging.

6.6 Special precautions for disposal and handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road, Erand Gardens,

Midrand, 1685

South Africa

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

Advantan cream : X/13.4.1/384

Advantan fatty ointment: X/13.4.1/386

Advantan ointment : X/13.4.1/385

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Advantan cream : 08 May 1992

Advantan ointment : 11 May 1992

Advantan fatty ointment: 11 May 1992

10. DATE OF REVISION OF THE TEXT

11 September 2023

Namibia:		
NS2	Advantan cream	04/13.4.1/1433
NS2	Advantan fatty ointment	04/13.4.1/1435
NS2	Advantan ointment	04/13.4.1/1434