SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ADVANTAN® MILK, 1 mg / g, Emulsion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g ADVANTAN® MILK 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 a preservative.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion.
White, opaque emulsion.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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).

4.2 Posology and method of administration

Posology

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 with the 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).

Paediatric population

No data are available.

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 of **ADVANTAN® MILK**.
- Tuberculous or syphilitic processes
- Viral infections (such as herpes or varicella),
- Rosacea, perioral dermatitis, ulcers, acne vulgaris, atrophic skin diseases and postvaccination skin reactions in the area to be treated.
- Bacterial and mycotic skin diseases (see section 4.4).
- 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® MILK** should not be used during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

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.

Local skin infections can be potentiated by topical glucocorticoid use.

As with all other glucocorticoids unprofessional use can mask clinical symptomatology.

Care must be taken when using ADVANTAN® MILK to avoid contact with the eyes, deep open wounds and mucosae.
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 (more than 40 % of the body surface). Nursing mothers should not be treated on the breasts (see section 4.6).
Topical corticosteroids should be used with particular caution in facial dermatoses, and only for short periods. Steroid rosacea-like facies may be produced.
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 as well as intertriginous areas might represent occlusive conditions.
As known from systemic corticoids, glaucoma may also develop from using local corticoids (e.g., after large-dosed or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin around the eyes).

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

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

ADVANTAN® MILK should not be applied to skin crease areas.
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.
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.

The excipient (caprylic-capric-myristic-stearic triglyceride) in ADVANTAN® MILK may reduce the effectiveness of latex products such as condoms and diaphragms.
This medicine contains 1,25 g benzyl alcohol in each 100 g. Benzyl alcohol may cause allergic reactions and/or mild local irritation.

Paediatric population
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.
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 Interactions with other medicines and other forms of interaction
None so far known.

Paediatric population
No information available.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no adequate data on the use of methylprednisolone aceponate in pregnant women.
Animal experimental studies with methylprednisolone aceponate have shown embryotoxic and/or teratogenic effects at doses which exceed the therapeutic dose (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 glucocorticoids during the first trimester of pregnancy.
In general, the use of topical preparations containing corticoids should be avoided during the

first trimester of pregnancy. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during pregnancy and lactation (see section 5.3).

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® MILK could result in sufficient systemic absorption of methylprednisolone aceponate to produce detectable quantities in human milk. Therefore, caution should be exercised when ADVANTAN® MILK is administered to a nursing woman.

Nursing mothers should not be treated on the breasts. Treating large areas, prolonged use or occlusive dressings should be avoided during lactation (see section 4.4).

Fertility

No information about the influence of methylprednisolone aceponate on fertility is available.

4.7 Effects on ability to drive and use machines

ADVANTAN® MILK has no influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

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.

In clinical studies, the most frequently observed side effect included application site burning.

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, <1/10); uncommon (≥1/1 000; <1/100), rare (≥1/10 000, <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data). The most appropriate MedDRA term was used to describe a certain reaction, its synonyms and related conditions.

b. Tabulated summary of adverse reactions

System organ class	**common**	**uncommon**	**not known**
Eye disorders			Vision blurred (see also section 4.4) *
Skin and subcutaneous tissue disorders		Eczema, skin exfoliation, skin fissures	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*
General disorders and administration site reaction	Application site burning	Application site pain, application site vesicles, application site pruritus, application site pustules, application site erosion	

* See also section 4.4.

c. Description of selected adverse reactions

As with other corticoids for topical application, the following local side effects may occur (frequency not known): skin atrophy, application site dryness and application site erythema, skin striae, application site folliculitis, hypertrichosis, telangiectasia, perioral dermatitis, skin discolouration, acne, and/or allergic skin reactions to any of the ingredients of the formulation. Systemic effects due to absorption may occur when topical preparations containing corticoids are applied.

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

4.9 Overdose

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

5.1 Pharmacodynamic properties

Category and class: A. 13.4.1 Corticosteroids without anti-infective agents.

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

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 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 adrenalin finally results in the vasoconstrictive activity of glucocorticosteroids.

Clinical efficacy and safety

A total of 716 patients aged from 4 months to 95 years were treated with ADVANTAN® MILK in 5 clinical trials. The main efficacy parameter in the clinical trials was the reduction of the total symptom score of the selected objective symptoms erythema, oedema, vesicles, papules, weeping and itching over the study period. The overall therapeutic success (complete healing and distinct improvement) in the clinical studies performed with ADVANTAN® MILK

once-daily treatment in patients with various types of eczema ranged from 82,5 % to 88,9 % (85 % on average).
Adverse events (AEs) occurred in 5 % of patients treated once daily with methylprednisolone aceponate. The occurring AEs were generally mild to moderate in intensity.

5.2 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.

5.3 Preclinical safety data

Systemic tolerance: 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® MILK has 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® MILK led to results typical for glucocorticoids, i.e., embryolethal and/or teratogenic effects are induced in the appropriate test system.

Genotoxicity: 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.
Tumorigenicity: 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® MILK under the recommended conditions of use, no influence on the occurrence of tumors is to be expected.

Local tolerance: In investigations into the 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.

Sensitisation: Methylprednisolone aceponate showed no sensitizing potential on the skin of the guinea pig.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium-chain
Caprylic-capric-myristic-stearic triglyceride
Macrogol-2-stearylether
Macrogol-21-stearylether
Benzyl alcohol
Disodium edetate
Glycerol (85 %)
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

After first opening of the tube, the in-use stability is 3 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Tubes of 20 g or 50 g made of polyethylene, white laminate tube and low-density film with aluminium layer. The shoulder is made of white polyethylene and has a white polypropylene re-closable screw cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

32/13.4.1/0362

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 February 2000

10. DATE OF REVISION OF THE TEXT

08 May 2023

Namibia: (NS2) 04/13.4.1/1436