# PROFESSIONAL INFORMATION

**SCHEDULING STATUS** S4

**1. NAME OF THE MEDICINE**
**ADVANTAN® SCALP SOLUTION**, 1 mg / mL solution

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
1 mL ADVANTAN® SCALP SOLUTION contains methylprednisolone aceponate (21-acetoxy-11β-hydroxy-6α-methyl-17-propionyloxy-1,4-pregnadiene-3,20-dione) 1 mg.

For full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**
Solution.
Clear, colourless, non-aqueous solution.

**4. CLINICAL PARTICULARS**
**4.1 Therapeutic indications**
Treatment of inflammatory and pruritic dermatoses of the hairy scalp, e.g. endogenous eczema (atopic dermatitis, neurodermatitis), seborrhoeic eczema, contact eczema, nummular eczema, vulgar eczema.

**4.2 Posology and method of administration**
**Posology**
ADVANTAN® SCALP SOLUTION is to be applied dropwise once daily to the affected areas and rubbed in lightly.

In general, the duration of use should not exceed 4 weeks.

**Paediatric population**
No data are available.

**Method of administration**
For external use only.

**4.3 Contraindications**
ADVANTAN® SCALP SOLUTION must not be used in cases of hypersensitivity to the active substance or to any of the excipients listed in section 6.1, presence of tuberculous or syphilitic processes, viral infections (such as herpes zoster or varicella), rosacea, perioral dermatitis, ulcers, acne vulgaris, atrophic dermatitis and vaccination skin reactions in the area to be treated.

Skin diseases associated with bacterial or fungal infections (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® SCALP SOLUTION 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.

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

To date, no clinical data are available for the use of ADVANTAN® SCALP SOLUTION in children.
Local skin infections can be potentiated by topical glucocorticoid use.

Care must be taken when using ADVANTAN® SCALP SOLUTION to avoid contact with the eyes, open wounds and mucosae. ADVANTAN® SCALP SOLUTION is flammable: it should not be applied near open flames.

No impairment of adrenal function has been observed in children after non-occlusive treatment with ADVANTAN® ointment on extensive skin areas (40-90 % of body surface area).
After application of ADVANTAN® hydrophobic cream to 60 % body surface under an occlusive dressing for 22 hours, suppression of plasma cortisol levels and influence on circadian rhythm was observed in adult healthy volunteers, therefore treatment duration should be kept as short as possible in these situations.

Extensive application of corticosteroids to large areas of the body or for prolonged periods of time, in particular under an occlusive dressing, significantly increases the risk of undesirable effects. Treatment with occlusive dressings should be avoided, unless otherwise indicated.
Note that nappies as well as intertriginous areas may act as an occlusive dressing. When treating large areas of the body, the duration of treatment should be kept as short as possible as the possibility of absorption or a systemic effect cannot be completely excluded.
As with all corticosteroids, inappropriate use can mask clinical symptomatology. As known from systemic corticosteroids, glaucoma can also develop from using corticosteroids for cutaneous use (e.g. after large-dosed or extensive application over a prolonged period, occlusive dressings, or application to the skin around the eyes).

*Visual disturbances*
Visual disturbances may be reported with the use of systemic and topical corticosteroids. 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.
The use of products for cutaneous use, especially if prolonged, can provoke sensitisation phenomena. In this case, treatment should be discontinued and appropriate treatment instituted.

The clinical indication for treatment with ADVANTAN® SCALP SOLUTION must be very carefully reviewed and the benefits weighed against the risks in lactating women.

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® SCALP SOLUTION should not be applied to skin crease areas.

**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 4.3).

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

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

**4.7 Effects on ability to drive and use machines**
ADVANTAN® SCALP SOLUTION has no influence on the ability to drive and use machines.

**4.8 Undesirable effects**
***a. Summary of the safety profile***
Occasionally, the alcohol content of the ADVANTAN® SCALP SOLUTION 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.

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 adverse reaction, its symptoms and related conditions.

***b. Tabulated summary of adverse reactions***

| System organ class | common | uncommon | not known* |
|---|---|---|---|
| **Eye disorders** | | | Vision blurred (see section 4.4) |
| **Skin and subcutaneous tissue disorders** | | Seborrhoea capitis, hair loss | Acne, telangiectasia, skin atrophy, skin striae, perioral dermatitis, skin discolouration, allergic skin reactions |
| **General disorders and administration site reaction** | Burning | Pruritus, pain, folliculitis, localised sensation of warmth, dryness, irritation, eczema | Blisters, erythema, hypertrichosis |

** Potential undesirable effects not observed in clinical trials.*

***c. Description of selected adverse reactions***
Systemic effects due to absorption may occur when topical preparations containing corticosteroids 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**
Please refer to sections 4.4 and 4.8.
Treatment should be discontinued if skin atrophy due to overdose of the topical preparation occurs. Symptoms normally resolve within 10 -14 days.
Results from acute toxicity studies with methylprednisolone aceponate 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 ingestion.
Effects related to isopropyl alcohol, a base component, can occur following inadvertent ingestion of ADVANTAN® SCALP SOLUTION. These effects can manifest as symptoms of depression affecting the central nervous system, even from ingesting only a few millilitres of the medicinal product.
If any symptoms of overdosage occur, treatment must be discontinued.

**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® SCALP SOLUTION 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.

**5.2 Pharmacokinetic properties**
Methylprednisolone aceponate becomes available in the skin after application of the ADVANTAN® SCALP SOLUTION 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).

The percutaneous absorption of methylprednisolone aceponate from ADVANTAN® SCALP SOLUTION was investigated after single application to volunteers and after once daily application for 4 weeks in patients with psoriasis capitis. ≤ 5 mL of the solution were applied once or daily onto the hairy scalp. A percutaneous absorption of methylprednisolone aceponate through the skin of the hairy scalp could not be demonstrated using a radioimmunological method for determination of methylprednisolone aceponate in the plasma.
Taking into consideration the detection limit of the radioimmunological method the systemic corticosteroid load caused by percutaneous absorption through the scalp in both trials was assessed to be less than 4 ng and 7 ng methylprednisolone aceponate equivalent/kg body weight and day, respectively.
After reaching the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, 6α- methylprednisolone-17-propionate is quickly conjugated with glucuronic acid and as a result, inactivated.
The metabolites of methylprednisolone aceponate (main metabolite: 6 α-methylprednisolone-17-propionate-21-glucuronide) are eliminated primarily via the kidneys with a half-life of about 16 hours. Following intravenous administration, excretion of the $^{14}$C-labelled substances with the urine and faeces was complete 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 administrations, methylprednisolone aceponate showed the action profile of a typical glucocorticoid.
It can be concluded from these results that following the therapeutic use of ADVANTAN® SCALP SOLUTION 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 under an occlusive dressing.

Embryotoxicity studies with ADVANTAN® SCALP SOLUTION led to results typical for glucocorticoids, i.e. specific embryotoxic effects and/or teratogenic effects are induced in the appropriate test system. The results of epidemiological studies are summarised in section 4.6.

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 tumour occurrence. As systemically effective immunosuppressive exposure is not reached with dermal application of ADVANTAN® SCALP SOLUTION under the recommended conditions of use, no influence on the tumour occurrence to be expected.

Results from local tolerance investigations, following topical application of methylprednisolone aceponate and ADVANTAN® SCALP SOLUTION formulations on the skin and mucosae, did not reveal any local side-effects other than those associated with glucocorticoid use.
Sensitisation: methylprednisolone aceponate showed no sensitising potential in guinea pigs.
Local atrophying power evaluated in controlled studies carried out in rat, rabbit and dog was found to be very low.

**6 PHARMACEUTICAL PARTICULARS**
**6.1 List of excipients**
Isopropyl myristate
Isopropyl alcohol

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
36 months.

**6.4 Special precautions for storage**
Store at or below 30 °C.
Keep well closed.

**6.5 Nature and contents of container**
Polyethylene dropper bottles of 20 mL or 50 mL.

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
South Africa
Customer Care: 0860 ADCOCK / 232625

**8. REGISTRATION NUMBER(S)**
32/13.4.1/0361

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
26 September 2001

**10. DATE OF REVISION OF THE TEXT**
07 September 2021

Namibia: NS2: ADVANTAN SCALP SOLUTION: 04/13.4.1/1475

adcock ingram