

# NEW ZEALAND DATA SHEET

## 1 ADVANTAN®

Cream: ADVANTAN® methylprednisolone aceponate 0.1% cream

Ointment: ADVANTAN® methylprednisolone aceponate 0.1% ointment

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g cream or ointment contains 1 mg (0.1%) methylprednisolone aceponate.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Topical cream.

Topical ointment.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Atopic dermatitis (endogenous eczema, neurodermatitis), contact eczema, degenerative, dyshidrotic, vulgar eczema, eczema in children.

### 4.2 Dose and method of administration

ADVANTAN® is for EXTERNAL TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

In general, 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.

### 4.3 Contraindications

ADVANTAN® is contraindicated in most viral diseases (e.g. vaccinia, varicella/herpes zoster) and when tuberculous or syphilitic processes and post-vaccination skin reactions are present in the area to be treated. If rosacea, acne vulgaris, ulcera, atrophic skin diseases, or perioral dermatitis are present, ADVANTAN® must not be applied to the face.

Hypersensitivity to the active substance or to any of the excipients listed in 6.1.

### 4.4 Special warnings and precautions for use

Care must be taken when using ADVANTAN® to avoid contact with the eyes, deep open wounds and mucosae.

Additional specific therapy is required in bacterially infected skin diseases and/or in fungal infections. Any spread of infection may require withdrawal of topical corticosteroid therapy.

If the skin dries out excessively under protracted use of ADVANTAN® Cream, a switch should be made to ADVANTAN® ointment, a formulation which has a higher fat content.

If signs of hypersensitivity develop, ADVANTAN® should be discontinued and appropriate treatment instituted.

## NEW ZEALAND DATA SHEET

Any of the side effects that have been reported following systemic use of corticosteroids, including adrenal suppression, may also occur with topical corticosteroids, especially in infants and children.

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. If either of the above is observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency.

Risk factors of increased systemic effects are:

- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (note that nappies can be occlusive)
- Increased hydration of the stratum corneum
- Use on thin areas such as the face
- Use on broken skin or other condition where the skin barrier may be impaired
- In comparison with adults, children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to the body weight ratio compared with adults. Use of topical corticosteroids in children should be limited to the least amount required for therapeutic effect. Chronic corticosteroid therapy may interfere with the growth and development of children.

However, to date, no impairment of adrenocortical function has been observed when used on large areas (40–60% of the skin surface) or even occlusive treatment with ADVANTAN® for up to 12 weeks in adults or 4 weeks in children.

Nevertheless, for the treatment of large areas duration of use should be kept as brief as possible.

Local atrophy, telangiectasia and striae may occur after prolonged treatment or excessive application. Treatment should be discontinued if symptoms such as cutaneous atrophy occur. Prolonged use on flexures and in intertriginous areas is undesirable.

ADVANTAN® Cream or Ointment should not be used around the eyes. The use of topical corticosteroids on the face can exacerbate rosacea and lead to peri-orofacial dermatitis. Patients should be warned against using ADVANTAN® on the face except on medical advice and any use on the face should be restricted to short periods.

As known from systemic corticoids, glaucoma may also develop from using local corticoids (e.g. after large doses or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin around the eyes).

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroid preparations

Two excipients contained in ADVANTAN® Cream (cetostearyl alcohol and butyl hydroxytoluene) may cause local skin reactions (e.g. contact dermatitis). Butyl hydroxytoluene may also cause irritation in the eyes and mucous membranes.

## NEW ZEALAND DATA SHEET

4.5 Interaction with other medicines and other forms of interaction  
None so far known.

4.6 Fertility, pregnancy and lactation  
Pregnancy

There is no adequate data from the use of ADVANTAN® in pregnant women. Animal experimental studies with methylprednisolone aceponate have shown embryonic and/or teratogenic effects (refer to the Preclinical safety data section). 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 of occlusive dressing should be avoided during pregnancy.

Epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with glucocorticosteroids during the first trimester of pregnancy.

Reduced placental and birth weight have been recorded in animals and humans after long-term treatment with topical corticosteroids. Since the possibility of suppression of the adrenal cortex in the newborn baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing these drugs. Maternal pulmonary oedema has been reported, with tocolysis and fluid overload.

As a general rule, topical preparations containing corticoids should not be applied during the first trimester of pregnancy. The clinical indication for treatment with ADVANTAN® must be carefully reviewed and the benefits weighed against the risks in pregnant and lactating women. In particular, treatment of large areas or prolonged use (greater than 4 weeks) must be avoided.

Breastfeeding

It is not known if methylprednisolone aceponate is secreted in human milk; systemically administered corticosteroids have been reported to appear in human milk. It is not known whether topical administration of ADVANTAN® could result in sufficient systemic absorption of methylprednisolone aceponate to produce detectable quantities in human milk. Therefore caution should be exercised when ADVANTAN® is administered to a woman who is breastfeeding.

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

4.7 Effects on ability to drive and use machines  
There is no effect.

4.8 Undesirable effects

In clinical studies, most frequently observed side-effects included burning and pruritus at the application site with ADVANTAN® Cream and Ointment.

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 available data). MedDRA version 12.0 was used for coding.

## NEW ZEALAND DATA SHEET

### ADVANTAN® Cream 0.1%

System organ class	Common	Uncommon	Rare
<b>General disorders and administration site reaction</b>	Application site burning, application site pruritus	Application site dryness, application site erythema, application site vesicles, application site folliculitis, application site rash, application site paraesthesia	Application site cellulitis, application site oedema, application site irritation
<b>Immune system disorders</b>		Drug hypersensitivity	
<b>Skin and subcutaneous tissue disorders</b>			Pyoderma, skin fissures, telangiectasia, skin atrophy, fungal skin infection, acne

- ADVANTAN® Ointment 0.1%

System organ class	Common	Uncommon	Not known (cannot be estimated from available data)
<b>General disorders and administration site reaction</b>	Application site burning, application site pruritus	Application site erythema, application site dryness, application site vesicles, application site irritation, application site eczema, application site papules, oedema peripheral	Application site cellulitis, application site oedema, application site irritation
<b>Skin and subcutaneous tissue disorders</b>		Skin atrophy, ecchymosis, impetigo, skin greasy	Acne

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, pruritus, local skin burning/skin pain, erythema, rash, urticaria, pustular psoriasis, allergic skin reactions/allergic contact dermatitis/dermatitis to any of the ingredients of the formulations. Systemic effects due to absorption may occur when topical preparations containing corticoids are applied. Although very rare, examples of systemic effects affecting the endocrine system or skin include hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushingoid features (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, osteoporosis, glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels, alopecia, trichorrhexis, skin thinning\*/skin atrophy\*, skin wrinkling\*, skin dryness\*, striae\*, telangiectasias\*, pigmentation changes\*, hypertrichosis, exacerbation of underlying symptoms eczema.

\*Skin features secondary to local and/or systemic effects of HPA axis suppression.

# NEW ZEALAND DATA SHEET

## 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 <https://nzphvc.otago.ac.nz/reporting/>

### 4.9 Overdose

#### Symptoms of intoxication

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Corticosteroids, potent (group III)

ATC code: D07AC14

### 5.1 Pharmacodynamic properties

After topical application, ADVANTAN® suppresses inflammatory and 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).

On application of methylprednisolone aceponate in topically effective dosage, the systemic effect is minimal in both man and animals. After large-area treatment of patients with skin disorders, levels of plasma cortisol remain within the normal range, circadian cortisol rhythm is maintained, and no reduction of cortisol has been ascertained in 24-hour urine.

As for all other glucocorticoids, 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 of the principal metabolite 6 $\alpha$ -methyl-prednisolone -17-proprionate, 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 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 epinephrine finally results in the vasoconstrictive activity of glucocorticoids.

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

## NEW ZEALAND DATA SHEET

- ADVANTAN® Cream

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

- ADVANTAN® Ointment

Skin conditions which are neither weeping nor very dry require a base with balanced proportions of fat and water. ADVANTAN® Ointment is suitable for dry, fissured, scaly or hyperkeratinised skin areas. It should not be used in areas such as axilla, groin or skin folds. ADVANTAN® Ointment makes the skin slightly greasy without retaining warmth and fluid. Of the three formulations, ADVANTAN® Ointment has the widest field of use.

### 5.2 Pharmacokinetic properties

Methylprednisolone aceponate (MPA) becomes available in the skin from all formulations (cream, ointment). 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 – an indication of “bioactivation” in the skin.

The degree of percutaneous absorption depends on the state of the skin, the formulation and the conditions of application (open/occlusion). Studies in juvenile and adult patients with neurodermatitis and psoriasis have shown that the percutaneous absorption on open application was only slightly ( $\leq 2.5\%$ ) greater than the percutaneous absorption in volunteers with normal skin (0.5–1.5%).

When the horny layer is removed before the application, the corticoid levels in the skin are about three times higher than after application to intact skin.

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

The metabolites of MPA (main metabolite: 6 $\alpha$ -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 <sup>14</sup>C-labeled 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 administration, MPA showed the action profile of a typical glucocorticoid. It can be concluded from these results that following therapeutic use of ADVANTAN® no side-effects other than those typical of glucocorticoids are to be expected, even under extreme conditions such as application over a large surface area and/or occlusion.

Specific tumourigenicity studies using MPA 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

# NEW ZEALAND DATA SHEET

ADVANTAN® under the recommended conditions of use, no influence on the occurrence of tumours is to be expected.

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 MPA.

Animal studies with MPA have shown embryo-lethal defects in rats dosed subcutaneously during the period of organogenesis at doses greater than 1 mg/kg/day and in rabbits following dermal application at doses greater than 0.25 mg/kg/day. No teratogenic effects were observed in rabbits, but in rats the incidences of ventricular septal defects and of cleft palate were increased at subcutaneous doses greater than 1 and 10 mg/kg/day. Similar embryo-lethal and teratogenic effects have been found with other corticosteroids and while not considered relevant to humans, particular care should be taken when prescribing ADVANTAN® during pregnancy.

In investigations into the local tolerance of MPA and ADVANTAN® formulations on the skin and the mucosa, no findings other than the topical side-effects known for glucocorticoids were recorded. MPA showed no sensitising potential on the skin of the guinea-pig.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Cream: decyl oleate, glycerol monostearate 40–55%, cetostearyl alcohol, hard fat, caprylic-capric-stearic acid triglyceride (Softisan 378), polyoxyl-40-stearate, glycerol 85%, disodium edetate, benzyl alcohol, butyl hydroxytoluene, purified water.

Ointment: beeswax (white), paraffin, liquid, Dehymuls E, paraffin (white soft), purified water.

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

Shelf life: 3 years

### 6.4 Special precautions for storage

Store below 25°C.

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

### 6.5 Nature and contents of container

Tubes containing 15 g.

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

### 6.6 Special precautions for disposal

None

## 7 MEDICINE SCHEDULE

Prescription Medicine

# NEW ZEALAND DATA SHEET

## 8 SPONSOR

LEO Pharma Limited

Auckland

New Zealand

Toll Free No. 0800 497 456

## 9 DATE OF FIRST APPROVAL

Cream and ointment: 26 March 1992

## 10 DATE OF REVISION OF THE TEXT

15 MAY 2023

## SUMMARY TABLE OF CHANGES

<b>Section affected</b>	<b>Summary of new information</b>
4.4	Updated Rebound Effects under Section 4.4
4.4	Updated HPA axis suppression under Section 4.4
4.8	Updated HPA axis suppression under Section 4.8