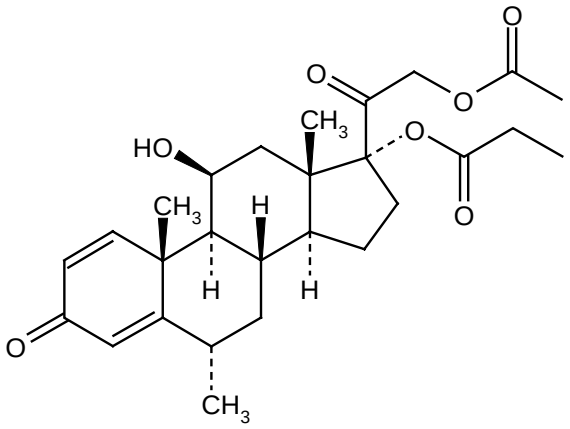
PRODUCT INFORMATION – ADVANTAN® OINTMENT, FATTY OINTMENT, CREAM & LOTION

NAME OF THE DRUG

The chemical name is 21-acetoxy-11β-hydroxy-6α-methyl-17-propionyloxy-1, 4-pregnadiene-3, 20-dione.

The chemical structure is



The CAS registry number is 86401-95-8. The molecular formula is $C_{27}H_{36}O_7$. The molecular weight is 472.58.

DESCRIPTION

The active ingredient of the Advantan® formulations is the synthetic corticosteroid methylprednisolone aceponate (MPA), which is a white crystalline powder. Methylprednisolone aceponate is soluble in methylene chloride, acetone and ethyl acetate and is sparingly soluble in hexane and ether.

Advantan® ointment is a water-in-oil emulsion containing 30% purified water. It also contains white soft paraffin, heavy liquid paraffin, white beeswax and Dehymuls E.

Advantan® fatty ointment is a monophasic ointment with 96.9% hydrocarbons (white soft paraffin, heavy liquid paraffin, microcrystalline wax) and hydrogenated castor oil.

Advantan® cream is an oil-in-water emulsion containing about 60% purified water. It also contains decyl oleate, glyceryl monostearate, cetostearyl alcohol, hard fat, Softisan 378, PEG-40 stearate, glyceryl 85%, butylated hydroxytoluene, benzyl alcohol, and disodium edetate.

Advantan® lotion is an oil-in-water emulsion containing 68% purified water. It also contains medium chain triglycerides, caprylic/capric/stearic triglycerides, steareth-2, steareth-21, benzyl alcohol, disodium edetate and glycerol.

PHARMACOLOGY

Pharmacodynamics

After topical application, Advantan® (methylprednisolone aceponate) has anti-inflammatory, anti-pruritic and vasoconstrictive actions.

As for all other glucocorticoids, the mechanism of action of methylprednisolone aceponate is not completely understood. It is known that methylprednisolone aceponate binds to the intracellular glucocorticoid receptor as does the principal metabolite 6α-methylprednisolone-17-propionate, which is formed by cleavage in the skin. The steroid-receptor complex binds to certain regions of DNA, inducing anti-inflammatory, anti-pruritic and vasoconstrictive effects.

Binding of methylprednisolone aceponate or its metabolites to the steroid receptor results in the induction of lipomodulin synthesis. Lipomodulin, a protein secondary messenger (also known as lipocortin 1 and macrocortin) inhibits release of arachidonic acid, which in turn inhibits the formation of inflammatory mediators, such as prostaglandins and leukotrienes.

The immunosuppressive action of glucocorticoids can be explained in part by their inhibitory effects on chemotaxis (inhibition of leukotriene synthesis). Glucocorticoids also have anti-mitotic activity, which is not well understood.

The vasoconstrictive activity of glucocorticoids results from the inhibition of prostaglandin synthesis. Prostaglandins have vasodilatory actions. Glucocorticoids also potentiate the vasoconstrictive effect of adrenaline.

Please note that the base formulations of the various Advantan® presentations influence the therapeutic effects (see **PRESENTATION**).

Pharmacokinetics

Methylprednisolone aceponate is bioavailable from all formulations (cream, ointment, fatty ointment and lotion). When applied topically the concentration of methylprednisolone aceponate is highest in the outer layer of the epidermis (stratum corneum) and decreases progressively in the deeper strata.

Methylprednisolone aceponate is hydrolysed in the epidermis and dermis to the principal metabolite, 6α-methylprednisolone-17-propionate. This metabolite binds to the intracellular glucocorticoid receptor with higher affinity than methylprednisolone aceponate. The binding of 6α-methylprednisolone-17-propionate to the receptor is an indicator of “bioactivation” in the skin.

Percutaneous absorption:
The degree of percutaneous absorption of methylprednisolone aceponate varies according to the state of the skin (intact/inflamed/damaged), the formulation (ointment/fatty ointment/cream/lotion) and the conditions of application (ope/occlusion). Studies using the ointment, fatty ointment and cream formulations in juvenile and adult patients with neurodermatitis and psoriasis have shown that the percutaneous

absorption on open application was slightly (≤2.5%) greater than the percutaneous absorption in volunteers with normal skin (0.2 – 1.5%). Occlusive dressing increased percutaneous absorption. When the superficial horny layer is removed before application of methylprednisolone aceponate, the corticoid levels in the skin are about three times higher than after application to intact skin.

Skin was artificially damaged to investigate the percutaneous absorption of methylprednisolone aceponate from the lotion formulation. Intact skin was compared with both artificially inflamed (UV-B erythema) and artificially damaged (removal of horny layer) skin. The absorption through artificially inflamed skin was very low (0.27%) and was only marginally higher than the absorption through intact skin (0.17%). The percutaneous absorption of methylprednisolone aceponate through artificially damaged skin resulted in higher levels of corticoid in the skin (15%).

Systemic absorption:
After absorption into the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, 6α-methylprednisolone-17-propionate, is rapidly conjugated with glucuronic acid, and as a result, inactivated.

The principal metabolites of methylprednisolone aceponate are eliminated primarily via the kidneys. The half-life is about 16 hours. Following intravenous administration, excretion via the urine and faeces was complete within 7 days. There is no accumulation of methylprednisolone aceponate or metabolites in the body.

The systemic effects of methylprednisolone aceponate are minimal in both man and animals following application of a topically effective dose. After treatment of large areas in patients with skin disorders, the plasma cortisol values remain within the normal range; circadian cortisol rhythm is maintained and no reduction of cortisol has been ascertained in 24-hour urine.

CLINICAL TRIALS

Topical treatment of eczema in adults using methylprednisolone aceponate 1mg/g lotion

The effectiveness of Advantan® lotion and other topical corticosteroids was measured by standardised clinical assessment of signs and symptoms from which a total (sum) score for comparison was derived. The observed difference (up to 20%) in comparative sum scores is considered within norms for observer variability, and not clinically meaningful. In clinical studies, where active treatment arms were compared, the ratio of effectiveness of the two treatments did not vary by more than 20%. The statistically significant equivalence band for 95% CI of ratios was 0.8-1.25.

One double-blind, multicentre, randomised, vehicle-controlled study assessed the efficacy and safety of methylprednisolone aceponate (MPA) lotion 1mg/g applied topically twice daily in patients with eczema. The study was 14 days duration. The primary efficacy endpoint was the total score of selected objective and subjective symptoms of eczema (erythema, oedema, vesicles, papules, weeping and itching). The mean total score at the end of treatment was statistically significant (p=0.001, one-sided) favouring MPA.

Table 1: Twice-daily administration of MPA 1mg/g lotion in adults

Treatment administered:		MPA lotion (n=99)	Vehicle (n=48)
Results:			
Total score (mean±sd)	Baseline:	14.5±3.9	14.6±4.2
	End:	8.2±3.7	10.0±5.4
		P=0.001 (one-sided)	

One double-blind, multicentre, randomised, vehicle-controlled study of 14 days duration assessed the efficacy and safety of MPA lotion 1mg/g applied twice daily versus amcinonide 0.1% lotion twice daily in patients with eczema. The primary efficacy endpoint was the total score of selected objective and subjective symptoms of eczema (erythema, oedema, vesicles, papules, weeping and itching). The mean total score at the end of treatment was statistically significant (p=0.036, one-sided) favouring MPA over placebo; MPA lotion was equivalent to amcinonide lotion (95% CI: 0.94, 1.11).

Table 2: Twice-daily administration of MPA 1mg/g lotion versus amcinonide lotion 0.1% in adults

Treatment administered:		MPA lotion (n=85)	Amcinonide lotion (n=81)	Vehicle (n=51)
Results:				
Total score (mean±sd)	Baseline:	14.8±3.3	15.0±3.5	15.7±3.7
	End:	7.5±2.4	7.8±2.8	9.1±4.3
		MPA vs vehicle p=0.036 (one-sided) MPA vs amcinonide: 95% CI: 0.94, 1.11		

One double-blind, multicentre, randomised study of 14 days duration assessed the efficacy and safety of MPA lotion 1 mg/g vs betamethasone 17-valerate 0.1% lotion in patients with eczema. MPA lotion was applied either once or twice daily, whereas betamethasone was applied twice daily. The primary efficacy endpoint was total score of selected objective and subjective symptoms of eczema (erythema, oedema, vesicles, papules, weeping and itching). At the end of treatment, MPA lotion was equivalent to betamethasone lotion.

Table 3: Administration of MPA 1 mg/g lotion versus betamethasone in adults

Treatment administered:		MPA lotion (OD) (n=146)	MPA lotion (BD) (n=94)	Betamethasone lotion (BD) (n=95)
Results:				
Total score (mean±sd)		16.1±3.9	15.6±3.9	15.7±4.1
Baseline:		8.1±3.0	7.6±2.3	7.0±1.8
	End:			
		MPA OD vs MPA BD:		95% CI: 0.94, 1.10
		MPA OD va betamethasone:		95% CI: 1.02, 1.20
		MPA BD vs metamethasone:		95% CI: 1.00, 1.20

OD – once daily; BD – twice daily

One double-blind, multicentre, randomised study assessed the efficacy and safety of MPA lotion 1 mg/g versus amcinonide 0.1% lotion in patients with eczema. MPA lotion was applied either once or twice daily, whereas amcinonide was applied twice daily. The study was of 14 days duration. The primary efficacy endpoint was the total score of selected objective and subjective symptoms of eczema (erythema, oedema, vesicles, papules, weeping and itching). At the end of treatment, MPA lotion was equivalent to amcinonide lotion.

Table 4: Administration of MPA 1mg/g lotion versus amcinonide lotion 0.1% in adults

Treatment administered:		MPA lotion (OD) (n=122)	MPA lotion (BD) (n=82)	Amcinonide lotion (BD) (n=83)
Results:				
Total score (mean±sd)	Baseline:	15.0±4.1	14.9±4.4	15.7±4.1
	End:	7.4±1.9	7.3±2.7	7.4±2.2
		MPA OD vs MPA BD: 95% CI: 0.93, 1.10		
		MPA OD vs amcinonide: 95% CI: 0.95, 1.14		
		MPA BD vs amcinonide: 95% CI: 0.97, 1.15		

Topical treatment of eczema in children using methylprednisolone aceponate 1mg/g lotion

One double-blind, multicentre, randomised study assessed the efficacy and safety of MPA lotion 1 mg/g versus hydrocortisone 17-butyrate 0.1% lotion in paediatric patients with eczema. MPA lotion was applied once daily, and hydrocortisone 17-butyrate was applied twice daily. The study was of 14 days duration. The primary efficacy endpoint was the total score of selected objective and subjective symptoms of eczema (erythema, oedema, vesicles, papules, weeping and itching).

At the end of treatment MPA lotion was equivalent to hydrocortisone 17-butyrate lotion (MPA vs hydrocortisone 17-butyrate: 95% CI: 0.88, 1.09).

Table 5: Administration of MPA 1 mg/g lotion versus hydrocortisone 17-butyrate lotion 0.1% in children

Treatment administered:		MPA lotion (OD) (n=72)	Hydrocortisone 17 – butyrate (BD) (n=73)
Results:			
Total score (mean±sd)	Baseline:	16.5±3.6	16.0±3.4
	End:	7.6±2.7	7.4±2.1
		95% CI: 0.88, 1.09	

INDICATIONS

Advantan® cream, ointment and fatty ointment are indicated for the topical treatment of eczema and psoriasis in adults and children.

Advantan® lotion is indicated for the topical treatment of eczema in adults and children.

CONTRAINDICATIONS

Advantan® is contraindicated in viral diseases (eg. 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 or perioral dermatitis are present, Advantan® must not be applied to the face.

Hypersensitivity to methylprednisolone aceponate or any component of the formulations.

Children under 4 months due to lack of experience.

PRECAUTIONS

FOR EXTERNAL USE ONLY.

Advantan® should not be allowed to come into contact with the eyes when being applied to the face.

Additional specific therapy is required in skin conditions infected with bacteria and/or fungi. Any spread of infection requires withdrawal of topical corticosteroid therapy.

If the skin dries out excessively under protracted use of Advantan® cream or lotion, a change should be made to one of the formulations with a higher fat content (Advantan® ointment or fatty ointment).

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

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.

As known from systemically administered corticosteroids, glaucoma may also develop from using topical corticosteroids (eg. after large-dose or extensive application over a prolonged period, application under occlusive dressings, or application to skin around or near the eyes).

Advantan® is a potent steroid formulated for topical application. As with all potent corticosteroids, the possibility of hypothalamic-pituitary-adrenal (HPA) axis suppression resulting from percutaneous absorption of methylprednisolone must be considered when initiating or reviewing therapy, as adequate studies are not available to define the degree of risk.

Treatment of large areas has been noted to produce some suppression of cortisol secretion, but plasma levels remain above the lower limit of the normal range and circadian rhythm is maintained. Nevertheless, when treating large areas the duration of use should be kept as brief as possible. 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. This is particularly important in children

who may absorb proportionately larger amounts of topical corticosteroid and thus be more susceptible to systemic toxicity.

Systemic absorption of topical corticosteroids will be increased if extensive body surface areas are treated or if the occlusive technique is used. Suitable precautions should be taken under these conditions or when long-term use is anticipated. In infants and children, plastic pants and napkins may act as occlusive dressings and increase absorption. Because of children's larger skin surface area to bodyweight ratio, paediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than adults. Chronic/long-term corticosteroid therapy may interfere with growth and development of children. Use of topical corticosteroids in children should be limited to the least amount required for therapeutic effect.

Local atrophy, telangiectasia and striae may occur after prolonged treatment or excessive application. Treatment should be discontinued if symptoms such as cutaneous atrophy occur (see also **ADVERSE REACTIONS**).

There was no sensitising effect or potential in animal studies.

Carcinogenicity/Mutagenicity
Animal studies to evaluate the carcinogenic potential of methylprednisolone aceponate have not been conducted. Other glucocorticoid drugs have been shown to cause hepatic tumours in rats, and it must be assumed that methylprednisolone aceponate would have similar activity. However, in humans epidemiological surveys of many years of systemic glucocorticoid therapy have not revealed any evidence for a tumourigenic action of this substance class.

Methylprednisolone aceponate did not elicit any genotoxic effects or chromosomal damage in *in vitro* and *in vivo* assays conducted in bacteria and mammalian cells.

Use in Pregnancy – Category C
Animal studies with methylprednisolone aceponate have shown embryolethal effects 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 incidence of ventricular septal defects and of cleft palate were increased at subcutaneous doses greater than 1 and 10 mg/kg/day. Similar embryolethal and teratogenic effects have been found with other corticosteroids and are not considered relevant to humans.

Reduced placental and birth weight have been recorded in animals and humans after long-term treatment. 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 foetus when prescribing these drugs. Maternal pulmonary oedema has been reported, with tocolysis and fluid overload.

The clinical indication for treatment with methylprednisolone aceponate must be carefully reviewed and the benefits weighed against the risks in pregnant and lactating women. Treatment of large areas or prolonged use (greater than 4 weeks) must be avoided.

Use in lactation
It is not known whether methylprednisolone aceponate is secreted in breast milk. Methylprednisolone aceponate should be used during lactation only if benefits outweigh the risks.

Nursing mothers should avoid treatment over large areas. Advantan® should not be applied to the chest area during breast feeding to avoid possible ingestion by infants.

When considering use during lactation, note that after systemic administration, very small amounts of glucocorticoid may be present in breast milk. There is only a slight risk of exposure to methylprednisolone aceponate in breast milk following maternal dermal application at therapeutic doses, because the systemic absorption of methylprednisolone aceponate is minimal.

Interaction with Other Drugs
No specific information exists on interactions with other medications.

ADVERSE REACTIONS

Local concomitant symptoms such as itching, burning erythema or vesiculation may occur in isolated cases under treatment with Advantan®. In clinical studies 5.4% of patients treated with Advantan® cream, 4.7% of patients treated with Advantan® ointment or fatty ointment and 3.9% of patients treated with Advantan® lotion experience such symptoms. Withdrawals associated with adverse events occurred in less than 1.5% of treated patients.

In general, atrophy of the skin, telangiectasia, striae or acneiform skin conditions can occur during therapy with potent corticoids when applied to large areas of the body (about 10% or more) or for prolonged periods of time (more than 4 weeks); these symptoms usually regress within 10 to 14 days of discontinuing treatment. However, during one 12-week clinical investigation of Advantan® cream, ointment or fatty ointment, none of these side effects expected of topical preparations containing potent corticoids occurred in adults. Similarly, none of these side effects occurred in children when treated for up to 4 weeks (See also **PRECAUTIONS**).

As with other corticoids for topical application, the following side effects may occur rarely: folliculitis, hypertrichosis, perioral dermatitis, skin discolouration, hypersensitivity to any of the ingredients of the formulations.

DOSAGE AND ADMINISTRATION

Advantan® is FOR EXTERNAL TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

The Advantan® formulation most appropriate to the skin condition should be used.

If the skin dries out excessively during treatment with Advantan® cream or lotion, a change should be made to one of the formulations with a higher fat content ie. Advantan® ointment or fatty ointment.

Advantan® ointment, fatty ointment & cream
Advantan® ointment, fatty ointment or cream should usually be applied as a thin coating once per day to the affected areas. In the treatment of psoriasis, twice daily application may be required.

The duration of use should be less than 12 weeks in adults and less than 4 weeks in children.

Advantan® lotion
Advantan® lotion should be applied sparingly once daily to the affected areas and rubbed in gently.

The duration of use should be less than 12 weeks in adults and less than 4 weeks in children.

OVERDOSAGE

Excessive dosing may occur with prolonged or intensive topical use. Refer **to ADVERSE REACTIONS** for further information.

Acute toxicity studies with methylprednisolone aceponate (namely oral ingestion, or single dermal application to a large area, under conditions favourable to absorption) do not indicate that any acute intoxication is expected.

Contact the Poisons Information Centre on 131 126 for further advice on overdosage management.

PRESENTATION

Advantan® formulations contain 0.1% methylprednisolone aceponate.

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 the axilla, groin or skin folds. Advantan® ointment makes the skin slightly greasy without retaining warmth and fluid. It is available in tubes of 5g, 10g, 15g, 30g, 50g or 100g.

Advantan® fatty ointment
Very dry skin and the chronic stage of skin conditions require an anhydrous base. Advantan® fatty ointment base has an occlusive effect. It is suitable for treatment of areas where the stratum corneum is particularly thick, such as the pressure areas of elbows, knees, palms and soles. It is available in tubes of 5g, 10g, 15g, 30g, 50g or 100g.

Advantan® cream
As a low-fat formulation with a high water content, Advantan® cream is suitable for acute and subacute weeping stages of eczema, for very greasy skin and for use on exposed or hirsute areas. It is available in tubes of 5g, 10g, 15g, 30g, 50g or 100g.

Advantan® lotion

Advantan® lotion's formulation confers cooling properties. It is intended primarily for the treatment of acute eczema, where acute inflammation and tenderness is present. Because it is the least occlusive of the Advantan® formulations, it is suitable for treatment of large areas and skin flexures, as well as hirsute regions. It is available in tubes of 20g or 50g.

STORAGE

Advantan® ointment or cream:	Store below 25°C.
Advantan® fatty ointment or lotion:	Store below 30°C.

When stored below 25°C, Advantan® ointment, cream and lotion are stable for 3 years from date of manufacture.

When stored below 30°C, Advantan® fatty ointment is stable for 5 years from date of manufacture.

Do not use beyond the expiry date on the package.

Do not use if the pack shows signs of damage or tampering.

NAME AND ADDRESS OF SPONSOR

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DATE OF TGA APPROVAL

7 December 2001

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