

# Research Review

## PRODUCT REVIEW

Methylprednisolone aceponate 0.1% ointment/cream [ADVANTAN®]

### About the Reviewer



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A graduate of Otago University, Dr Jennifer Pilgrim undertook postgraduate training at Wadsworth VA-UCLA, California and St John's Hospital, London. She practices as a specialist dermatologist at Bowen Hospital, Wellington and also at Victoria University Student Health Service. Jennifer has extensive experience in a wide range of dermatological areas including paediatric and adolescent dermatology, minor surgery, tattoo removal, vulval disorders and some cosmetic procedures.

### About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key New Zealand specialist with a comment on the relevance to New Zealand practice.

Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of methylprednisolone aceponate 0.1% ointment/cream [ADVANTAN®], a fourth-generation, non-halogenated topical corticosteroid approved for use in New Zealand for the management of atopic eczema. Methylprednisolone aceponate has the advantage of once-daily dosing, providing benefits in terms of patient compliance, and has an optimised efficacy/safety profile with minimal local or systemic adverse effects. This agent is suitable for use in adults and children and also for short-term use on the face. This review focuses largely on the use of methylprednisolone aceponate in children with atopic eczema. Methylprednisolone aceponate 0.1% ointment/cream is fully funded by Pharmac.

### Atopic eczema

Atopic eczema (also known as atopic dermatitis) is a chronically relapsing, intensely pruritic inflammatory skin disease which favours flexural skin.<sup>1</sup> The condition typically develops in childhood, with approximately 80% of cases developing before the age of 5 years.<sup>2</sup> In the acute phase of the disease, erythema, vesicles, papules, crusts and weeping may be present, while in the chronic phase, lichenification and scaling of the skin are the predominant features.<sup>3</sup>

Evidence suggests that approximately 60% of childhood eczema cases are free of symptoms by early adolescence, but symptoms may recur in adulthood, often as hand eczema.<sup>1</sup> Children with early-onset, severe atopic eczema associated with asthma and/or hay fever tend to have a worse prognosis.<sup>1</sup> One-third of community cases of atopic eczema are in adults.<sup>1</sup> Overall, approximately 80% of cases of atopic eczema in the community are mild.<sup>1</sup>

Individuals with atopic eczema often have an inherited 'atopic tendency', meaning that they may develop closely linked conditions such as asthma and rhinoconjunctivitis, although 20% of individuals with a clinically typical atopic distribution of eczema are not atopic.<sup>1,4</sup>

### Prevalence

The overall prevalence of atopic eczema is 2-5%, with a prevalence of approximately 10-20% in children and young adults, thus making it the most common skin disease.<sup>1,4-8</sup> A 2001 NZ study reported an atopic eczema prevalence in children aged 6-7 years of 15% and a prevalence of 13% among those aged 13-14 years.<sup>6</sup>

### The burden of atopic eczema

Considerable physical and emotional morbidity may be present for the child with atopic eczema and his/her family, especially if the disease is poorly controlled.<sup>1,9-12</sup> In fact, an Australian study has shown that family stress related to the care of a child with moderate or severe atopic eczema is significantly greater than that for families of children with insulin-dependent diabetes mellitus.<sup>11</sup>

There are many factors that contribute to reduced quality of life for sufferers and their families, including itching, soreness, psychological issues, physical issues, time involved in applying creams, frequent visits to the doctor, dietary issues and sleep loss due to the constant itch associated with the condition.<sup>1,11,13</sup> A NZ survey found that 14% of children and 16% of adolescents with atopic eczema had their sleep disturbed at least one night per week by their condition.<sup>6</sup> Another study revealed a mean of 1-2 hours of sleep lost each night for both sufferers and parents of those with moderate or severe forms of the condition.<sup>11</sup> It has also been shown that on average, individuals with severe atopic eczema take 5.3 days off school or work per year because of their disease and, while experiencing a flare, their concentration is significantly affected.<sup>12</sup>

The economic costs associated with atopic eczema are high for both patient and community.<sup>1</sup> In Australia, it is estimated that the total cost of treating children with chronic eczema is \$A316.7 million per year (this cost does not take into account treating children with recent-onset eczema).<sup>7</sup>

### Diagnosis

The diagnosis of atopic eczema is a clinical one based on itching, redness and skin crease involvement, and takes into account the atopic stigmata of the condition.<sup>14</sup> The UK National Institute for Health and Clinical Excellence (NICE) 2007 guidelines recommend using the criteria outlined in **Figure 1** for diagnosing atopic eczema in children.<sup>14</sup> The guidelines, which have taken into account all available severity tools (including the Eczema Area and Severity Index [EASI]), recommend that healthcare professionals adopt a holistic approach when assessing the severity of a child's atopic eczema (**Table 1**).<sup>14,15</sup> This assessment should guide treatment decisions.

**Table 1: Assessing the severity of atopic eczema**

Skin/physical severity		Impact on quality of life and psychosocial wellbeing
<b>Clear</b>	Normal skin, no evidence of active atopic eczema	No impact on quality of life
<b>Mild</b>	Areas of dry skin, infrequent itching (with or without small areas of redness)	Little impact on everyday activities, sleep and psychosocial wellbeing
<b>Moderate</b>	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
<b>Severe</b>	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

(Adapted from UK NICE clinical guidelines<sup>4</sup>)

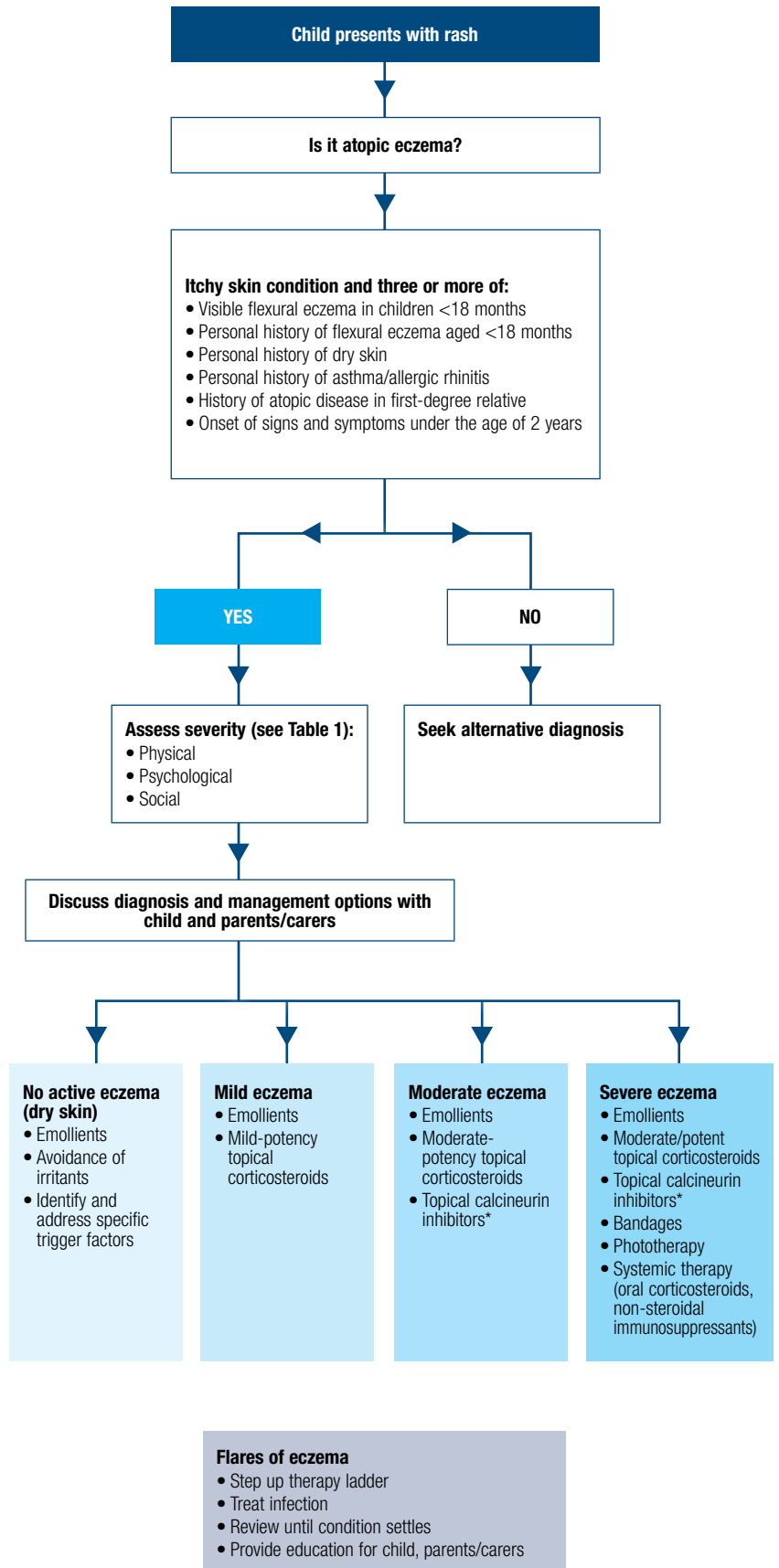
## Treatment options

As with other chronic conditions, the management plan for atopic eczema requires a multidisciplinary approach directed at long-term stabilisation, the prevention of flares and the avoidance of adverse effects.<sup>4</sup> Trigger factors such as irritants, contact allergens, food allergens and/or inhalant allergens need to be identified and managed, and treatment must be planned with a long-term perspective. Treating an exacerbation of atopic eczema involves efficient short-term control of acute symptoms and can be a therapeutic challenge.<sup>4</sup>

Mild cases of atopic eczema may be managed by avoiding sources of irritation and using emollients, which should be continued even when the skin is clear.<sup>14</sup> In the UK, current first-line treatment of atopic eczema involves the use of emollients, topical corticosteroids and antihistamines.<sup>1</sup> Second-line treatments include ultraviolet light therapy (although this is not used in NZ for children) and allergen avoidance.<sup>1</sup> Third-line treatments include systemic immunomodulatory agents (including azathioprine and cyclosporin A).<sup>1</sup>

International guidelines recommend that a stepped approach to management be employed, with treatment tailored to the severity of the condition (see **Figure 1**).<sup>14-16</sup> Treatment should be stepped up or down according to clinical response. Always use emollients, even when the skin is clear and add other treatments when required, with specialist advice where recommended (see page 6). Patients and their caregivers should be given advice on the quantities and frequency of treatments to be used and informed about recognising symptoms of bacterial and viral infection. A useful personal eczema management plan for patients with eczema is available from: <http://tinyurl.com/98wcqff>

Emollient therapy is crucial for maintaining skin hydration and improving skin barrier function, and is usually achieved by at least twice daily application of a moisturiser.<sup>4</sup> The use of emollients has been shown to significantly reduce the amount of topical corticosteroids used in infants with atopic eczema.<sup>17</sup> The jury seems to be out regarding the timing of the application of topical corticosteroids and emollients in conjunction with each other and, to date, no controlled trials have investigated this issue.



**Figure 1: Treatment algorithm for the diagnosis and treatment of paediatric atopic eczema.** (Adapted from UK NICE clinical guidelines<sup>4</sup>)

\*Pimecrolimus cream [Elidel<sup>®</sup>] is the only topical calcineurin inhibitor approved for use in NZ for atopic eczema. The agent is not funded in NZ.

## Topical corticosteroids

Mild atopic eczema may be managed sufficiently with emollients, but anti-inflammatory agents such as topical corticosteroids are required for moderate-to-severe symptoms resulting from acute flares and possibly for maintaining remission (when used intermittently). Topical corticosteroids, which are divided into four groups according to their strength (Class 1-4, see below), have been the gold standard in the treatment of atopic eczema for more than five decades. In treating atopic eczema the weakest possible steroid that will do the job should be used. However, at times it may be necessary to use a more potent corticosteroid to clear the skin. The NICE guidelines state that short treatment with a potent topical corticosteroid is as effective as a longer treatment with a mild preparation.<sup>14</sup> These agents are considered to be effective and safe when used correctly.<sup>1</sup> The following topical corticosteroids are available in NZ (some are available in combination with antibacterial or antifungal agents). Creams may be more suitable if the problem area is weeping, while ointments are recommended for drier areas. Lotions are more suitable for hairy areas. Continuous use for less than 1 month is considered short-term use, while use for greater than 3 months is considered long-term use.

### Class 1 (very potent):

- Clobetasol propionate
- Betamethasone dipropionate (in optimised vehicle)

### Class 2 (potent):

- Methylprednisolone aceponate
- Mometasone furoate
- Betamethasone valerate
- Betamethasone dipropionate
- Diflucortolone valerate
- Hydrocortisone 17-butyrate

### Class 3 (moderate):

- Clobetasone butyrate
- Triamcinolone acetonide

### Class 4 (mild):

- Hydrocortisone

## Therapeutic index

Methylprednisolone aceponate has been awarded an excellent therapeutic rating by the German Society of Dermatology who have published a Therapeutic Index (TIX) for a number of topical corticosteroids.<sup>18</sup> The TIX describes the balance between the efficacy of a topical corticosteroid and its adverse effects (see **Table 2**).

**Table 2: The benefit-to-risk ratio as assessed by the Therapeutic Index (TIX) published by the German Society of Dermatology for a selection of Class 1 and 2 topical corticosteroids**

Topical corticosteroid	Efficacy score	Toxicity score	TIX rating
Methylprednisolone aceponate	18.0	9.0	2.0
Mometasone furoate	18.0	9.0	2.0
Clobetasol propionate	27.0	17.0	1.5
Hydrocortisone butyrate	14.0	10.0	1.4
Betamethasone valerate	18.0	15.0	1.2

(Adapted from Ruzicka et al 2006)<sup>18,19</sup>

## Duration of topical corticosteroid use

Mild atopic eczema may respond to low-potency topical corticosteroids within a few days, with symptoms clearing within 1-2 weeks.<sup>20</sup> Moderate disease may require more potent topical corticosteroids and these may need to be used for several weeks to clear symptoms.<sup>20</sup> Severe disease may only partially respond to potent topical corticosteroids after several months.<sup>20</sup> The NICE guidelines also suggest considering treating problem areas with topical corticosteroids for two consecutive days per week (often referred to as 'weekend therapy') in order to prevent flares in children experiencing 2-3 flares per month (this strategy should be reviewed for effectiveness within 3 to 6 months).<sup>14</sup>

## Treatment compliance issues

Poor compliance with therapy is a major issue in treating patients with atopic eczema. Interestingly, the strongest predictor of treatment compliance is a good parent-doctor relationship.<sup>15,21,22</sup> Furthermore, a survey has shown that steroid phobia is a major contributor to poor treatment compliance and while the majority of patients receive topical corticosteroids to treat flares, 49% are concerned about using these agents.<sup>12,23</sup> Therefore, it is crucial that patients and their families are provided with simple, clear, unambiguous information on the management of this disease and are adequately educated regarding the risks and benefits of corticosteroid use.<sup>7,15,24</sup> Using topical corticosteroids that are dosed once daily as opposed to twice daily provides benefits in terms of patient compliance.

## About methylprednisolone aceponate

Methylprednisolone aceponate 0.1% topical ointment or cream [Advantan®] is a fourth-generation, non-halogenated corticosteroid, available in NZ and approved by Medsafe for the management of atopic eczema in children and adults; specific indications include endogenous eczema, neurodermatitis and contact eczema.<sup>25</sup> The agent is fully funded by Pharmac and has a list price of NZ\$4.95 per 15g tube. Clinicians may prescribe as many 15g tubes as deemed necessary for up to 3 months of treatment (see Prescribing Advantan® section below for advice on determining the amount required).

## Efficacy data

Methylprednisolone aceponate, dosed once daily, is considered to be a safe and effective acute and maintenance treatment choice for children (including infants) and adults with moderate-to-severe atopic eczema requiring fast and effective relief from their symptoms.<sup>3,19,26-30</sup> Its onset of activity is very rapid, with 50-80% of patients experiencing complete or distinct symptom improvement within 1 week of starting treatment and 90% experiencing such improvement within 3 weeks.<sup>3</sup> This is also true for patients with severe symptoms, who have been shown to experience fast and effective relief from reddening and itching.<sup>3</sup>

Methylprednisolone aceponate compares favourably with other corticosteroids in its class and to tacrolimus.<sup>3,19,26-30</sup> The efficacy and tolerability of once daily methylprednisolone aceponate was shown to be equivalent to that of betamethasone valerate dosed twice daily in patients with various forms of eczema, with success rates of >85%.<sup>19,31</sup> Furthermore, a randomised, double-blinded comparative study comparing methylprednisolone aceponate 0.1% ointment once daily (n = 129) and the calcineurin inhibitor tacrolimus 0.03% ointment applied twice daily (n = 136) for 3 weeks in children and adolescents with severe to very severe flares of atopic eczema revealed a successful therapy rate in both groups of 67%.<sup>26</sup> Notably in that study, an approximate 70% reduction in itch was seen with methylprednisolone aceponate after 7 days and the agent was superior to tacrolimus for EASI, itch and sleep measures.

Another study investigating the long-term management of moderate-to-severe atopic eczema in 221 individuals aged ≥12 years revealed that the agent applied twice weekly for 16 weeks along with an emollient effectively controlled the disease with a significantly reduced risk of relapse and no apparent adverse effects.<sup>32</sup>

## Safety data

The overall incidence of adverse effects associated with methylprednisolone aceponate is approximately 5% and this agent exhibits a low incidence of systemic adverse effects.<sup>3</sup> When adverse effects do occur they are almost always mild-to-moderate in severity and do not usually result in the discontinuation of treatment.<sup>3</sup> The most commonly seen adverse effects are mild erythema, dryness and a sensation of burning, scaling and rash.<sup>3,28</sup>

A number of studies have demonstrated that the incidence and severity of adverse effects with methylprednisolone aceponate are similar to those of less potent corticosteroids and significantly lower than those of other corticosteroids in the same class.<sup>3</sup> One such study was undertaken by Kecskés comparing methylprednisolone aceponate and mometasone furoate.<sup>33</sup> Their study revealed equal anti-inflammatory activity of the two agents and similar cortisol suppression, but significantly fewer local adverse effects with methylprednisolone aceponate than mometasone furoate.

The favourable safety profile of methylprednisolone aceponate renders it a suitable agent for use in facial eczema, and postmarketing surveillance has confirmed the very good efficacy and tolerability of this agent when used for this indication.<sup>34</sup> The development of perioral dermatitis is not likely if use of the agent beyond clinical healing is avoided.<sup>34</sup>

## Contraindications

Contraindications to the use of methylprednisolone aceponate include most viral diseases (e.g. varicella/herpes zoster, vaccinia), and the presence of syphilitic or tuberculous processes and post-vaccination skin reactions in the area to be treated.<sup>25</sup>

## Pharmacological properties

Methylprednisolone aceponate has a methyl group at C-6 and both of the alcohol residues attached to the five-membered ring (a propionate group at C-17 and an acetate group at C-21) are esterified.<sup>3</sup> The methyl group at C-6 is associated with a high intrinsic activity (drug-receptor binding), while the lipophilic diester grouping allows for good penetration into the stratum corneum.<sup>29</sup> The degree of penetration depends on the state of the skin and the conditions of application (open/occlusion).<sup>25</sup> Within the epidermis and dermis, methylprednisolone aceponate is rapidly metabolised by esterases to the active metabolite methylprednisolone-17-propionate, which binds 3-fold more strongly to glucocorticoid receptors than methylprednisolone aceponate.<sup>3</sup> Inflamed skin with its higher concentration of esterases, has been found to concentrate this active metabolite.<sup>3</sup> Within the skin, methylprednisolone-17-propionate is converted to methylprednisolone-21-propionate, which is hydrolysed and rendered relatively inactive.<sup>3</sup> Glucuronic acid rapidly inactivates any methylprednisolone-17-propionate entering the systemic circulation.<sup>3</sup> These metabolites are eliminated via the kidneys with a half-life of approximately 16 hours.<sup>25</sup>

Unlike other potent corticosteroids, methylprednisolone aceponate does not have a halogen at C-9 and this feature allows for the high degree of dissociation between topical and systemic effects; non-halogenated corticosteroids appear to preserve the function of the circadian rhythm of cortisol secretion even when used on large areas (40-60% of the skin surface).<sup>25,29,30</sup>

## Dosage and administration<sup>25</sup>

One gram of cream or ointment contains 1mg (0.1%) methylprednisolone aceponate. The agent is for external topical use only. Generally, the formulation deemed most appropriate to the skin conditions is applied thinly once daily and should be used for no more than 12 weeks in adults and no more than 4 weeks in children. The cream formulation of Advantan<sup>®</sup> has a high water content and a low fat content and is particularly suitable for the weeping stages of eczema. The ointment formulation of Advantan<sup>®</sup> is suitable for skin that is dry. When being applied to the face, the agent should only be used for short periods and must not come into contact with the eyes. If signs of hypersensitivity or skin atrophy occur the agent should be discontinued. Use in children should be limited to the least amount required for therapeutic effect. Prolonged use in intertriginous areas and on flexures is undesirable. If fungal or bacterial infections are present, additional specific therapy is required.

Bpac<sup>™</sup> best practice recommendations point out that underuse of topical corticosteroids is far more common than overuse.<sup>35</sup> They recommend using 'fingertip units' (FTUs) as a measure for dosing, with one FTU being the amount of product that can be squeezed onto the top third of an adult finger and equating to approximately 0.5g. See **Figure 2** for dosing using FTUs.

ADULT (in FTUs)					
	Face & neck	Arm & hand	Leg & foot	Torso (front)	Back
Adult	2.5	Arm: 3.0 Hand: 1.0	Leg: 6.0 Foot: 2.0	7.0	7.0
CHILD (in FTUs)					
Age	Face & neck	Arm & hand	Leg & foot	Torso (front)	Back & bottom
3-6 months	1.0	1.0	1.5	1.0	1.5
1-2 years	1.5	1.5	2.0	2.0	3.0
3-5 years	1.5	2.0	3.0	3.0	3.5
6-10 years	2.0	2.5	4.5	3.5	5.0

**Figure 2: Fingertip units (FTUs) for different areas of the body.**

One FTU is the amount of cream/ointment that can be squeezed onto the top third of an adult finger (approximately 2.5cm). ADVANTAN's 15g tube dispenses approximately 0.5g per FTU

## How much should I prescribe?

As a rough guide, if a 6-10 year-old child has the ointment or cream applied to their leg and foot once daily, they will require 4.5 FTUs per day (2.25g per day), equating to 15.75g of product per week. For this child, it would be appropriate to prescribe one tube of Advantan<sup>®</sup> per week for up to 4 weeks. An adult patient would require 8 FTUs to cover their leg and foot once daily (4g per day) and would thus require 28g of product per week, or eight tubes of Advantan<sup>®</sup> if a 4-week course is needed. These amounts are for one limb and so would need to be doubled for a bilateral presentation. Some patients requiring multiple tubes may be tempted to dispense them into a single container for ease of use. This should be discouraged as it has an unknown effect on the efficacy and safety of the product.

## Efficacy and safety of methylprednisolone aceponate 0.1% ointment/cream in major clinical trials

### Clinical experience with methylprednisolone aceponate (MPA) in eczema<sup>36</sup>

**Author:** Fritsch P

**Summary:** The efficacy of once or twice per day methylprednisolone aceponate (cream or ointment) was examined in six, multicentre, double-blind controlled trials in comparison with twice per day betamethasone valerate (cream) in a total of 1723 eczema patients (mean age ~45 years) over a period of up to 3 weeks. All regimens were found to be equally effective; >90% of patients were asymptomatic (erythema, vesiculation, weeping, crusting, scaling, lichenification) or greatly improved after 3 weeks. There were no differences between methylprednisolone aceponate and betamethasone valerate treatment, between cream and ointment formulations nor between once- and twice-daily application. Systemic side effects were not reported, while mild to moderate local complaints (itching, burning, erythema, dryness and scaling) were reported in 5.1 % of methylprednisolone aceponate recipients and 6.2% of betamethasone valerate recipients. Discontinuation for 'lack of efficacy' occurred in 1.6% of methylprednisolone aceponate and 0.7% of betamethasone valerate recipients.

**Comment:** There seems to be a lot of variables in this study, which makes it rather confusing. There is also no indication of the type of eczema treated, as acute vesicular eczema would be expected to respond differently from chronic lichenified eczema when using a cream rather than ointment formulation. It does support the safety and efficacy of methylprednisolone aceponate. It also confirms the current protocol of once daily use being appropriate.

### Effectiveness of topical methylprednisolone aceponate in eczema patients: results of the Swiss multicentre phase IV study<sup>28</sup>

**Author:** Elsner P

**Summary:** Use of methylprednisolone aceponate as a cream, ointment or fatty ointment was examined in a multicentre phase IV trial (average duration of treatment was 5 weeks) in 830 Swiss eczema patients ranging in age from 6 months to 97 years. Symptoms were cured or improved (investigator opinion) significantly in 87.4% of patients and with a response that was classified as fast or very fast onset in 79.4%; treatment discontinuation due to lack of efficacy occurred in 7.4% of patients. Patient tolerance was judged to be good or excellent in 92.3% of patients, although treatment was discontinued due to adverse events in 1.8% of patients.

**Comment:** We do not have a fatty ointment formulation of methylprednisolone aceponate in NZ. The safe use of the product in very young infants is reassuring. It would be helpful to have information about which patients did not respond. Patients seem to have been included with types of eczema which would not generally be managed with methylprednisolone aceponate (e.g. acute contact dermatitis and seborrhoeic dermatitis). There is also no information about concomitant treatment with emollients. This would be helpful to elucidate treatment failures.

## Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study<sup>32</sup>

**Authors:** Peserico A et al

**Summary:** The long-term efficacy (16 weeks) of methylprednisolone aceponate 0.1% cream twice weekly, in addition to an emollient (Advabase<sup>®</sup>), was examined in a multicentre, randomised, double-blind, controlled study of 249 patients after stabilisation of an acute severe or very severe flare of atopic dermatitis with methylprednisolone aceponate alone. Time to relapse (primary endpoint) of atopic dermatitis was longer in the methylprednisolone aceponate group than in the emollient only group, and the probability of being relapse free at 16 weeks was 87.1% in the methylprednisolone aceponate group versus 65.8% in those receiving emollient only. Methylprednisolone aceponate twice weekly induced a 3.5-fold lower risk of relapse than emollient alone (hazard ratio 3.5, 95% CI 1.9-6.4;  $p < 0.0001$ ). Methylprednisolone aceponate was also superior to emollient for all other efficacy endpoints (relapse rate, disease status, patient's assessment of intensity of itch, the EASI, Investigator's Global Assessment score, affected body surface area, Dermatology Life Quality Index (DLQI) and children's DLQI, patient's and investigator's global assessment of response and patient's assessment of sleep quality). Both treatments were well tolerated, with the frequency of adverse events with the emollient alone being higher than with the study drug (24% vs 15%); none of the adverse events reported during the maintenance phase were considered to be due to the study drug, and no serious adverse events were reported.

**Comment:** The use of maintenance therapy to prolong remissions is not well documented. Generally, once the eczema is under control topical steroids are discontinued and only reinstated when a flare occurs. Given the high safety profile and patient tolerance of the medication, this is a useful management suggestion. It is a bit surprising that the rate of adverse effects is higher with the emollient base (Advabase<sup>®</sup>) as this must be the base of the active medication.

## Effectiveness and tolerability of methylprednisolone aceponate (Advantan<sup>®</sup>) in the treatment of eczematous disorders of the face<sup>34</sup>

**Authors:** Ruzicka T and Zaumseil RP

**Summary:** The tolerability of methylprednisolone aceponate cream and/or ointment once daily for a maximum of 4 weeks was examined in a multicentre, post-marketing surveillance study in 575 patients (aged 3 months to 87 years) with eczematous dermatitis of the face (primarily neurodermatitis [46%] and contact eczema [25%]). Methylprednisolone aceponate was generally well tolerated, no skin infections or atrophy were reported and "very good tolerability" was reported by 86% of patients and 89% of doctors. Efficacy of methylprednisolone aceponate, based on doctor's assessment at the end of therapy, was "asymptomatic" in 66.3% of patients and "distinct improvement" in 32.9%.

**Comment:** I am not certain what a diagnosis of neurodermatitis implies and whether cream and ointment are being used in the same patient. The tolerability and efficacy of the product indicates its usefulness in facial dermatoses.

## Methylprednisolone aceponate (MPA) - use and clinical experience in children<sup>27</sup>

**Author:** Rampini E

**Summary:** In order to assess the clinical efficacy and tolerability of 0.1% methylprednisolone aceponate cream and ointment once or twice daily for a maximum of 21 days, two double-blind, multicentre clinical studies were performed in children aged  $\leq 14$  years suffering from atopic dermatitis and compared with treatment with 0.25% prednicarbate. An additional trial examined the systemic safety (endogenous cortisol production after 7 days application over a large skin area [mean 12.2% of skin surface]) of 0.1% methylprednisolone aceponate to 0.1% hydrocortisone 17-butyrate. There was no significant difference in response rates between methylprednisolone aceponate (once daily 96.3%; twice daily 97.4%) and prednicarbate (once daily 98.1%; twice daily 100%) in the efficacy trials ( $n = 108$  and  $78$ ), while the cortisol levels were unchanged after 7 days exposure to either methylprednisolone aceponate (14.22 vs 13.03  $\mu\text{g/dL}$ ) or 0.1% hydrocortisone 17-butyrate (11.70 vs 12.12  $\mu\text{g/dL}$ ). In the efficacy trials, a total of 36 children aged  $\leq 3$  years were treated with methylprednisolone aceponate or prednicarbate. The response rate in both groups was 100%.

**Comment:** Prednicarbate is not available in NZ. The response rates comparing once daily with twice daily use confirm the NZ guidelines on once daily use regime. Being able to reassure parents that there is no evidence of systemic absorption after 21 days (and therefore any systemic side effects) will go a long way in improving compliance. More prolonged use data would be interesting, but with the high response rate, use is generally for short periods only.

## Methylprednisolone aceponate in eczema and other inflammatory skin disorders – a clinical update<sup>19</sup>

**Author:** Ruzicka T

**Comment:** This is a useful overview of methylprednisolone aceponate with regards dosing regime, safety (both locally and systemically), tolerability and efficacy. It confirms the use of once-daily treatment being efficacious in a wide range of age groups and this, in conjunction with the rapid onset of improvement, increases compliance. The safety profile in terms of local tolerability and systemic effects are well documented. Studies on the suppression of the hypothalamic-pituitary axis show minimal effects, giving it a reassuring advantage in long-term use in children. This review also documents its safety and efficacy in a wide range of facial dermatoses, but the benefits of its use for the scalp is not relevant in NZ where we have no access to the milk formulation or the alcohol solution.

## Take-home messages

- Methylprednisolone aceponate is a useful agent in the management of atopic eczema in paediatric and adult populations
- Methylprednisolone aceponate has a high efficacy to safety ratio compared with topical steroids of similar potency
- The increased compliance with once daily dosing, as opposed to twice daily, is also significant (time taken to apply products repeatedly is acknowledged by patients as a reason for treatment failure)
- Patients are often reluctant to use ointment-based products as they are sticky, harder to apply (so more time consuming) and leave greasy residue on clothing and bedding
- Ointments are often superior in terms of hydration and efficacy
- Methylprednisolone aceponate ointment has the property of an ointment, but the cosmetic acceptability and ease of application of a cream

## Questions frequently asked by GPs

### When should I refer to a specialist dermatologist?

- Immediate (same day) referral to a specialist dermatologist should be sought if eczema herpeticum is suspected.
- Urgent referral (within 3 weeks) should be undertaken if atopic eczema is severe or failing to respond to 2 weeks of optimal topical therapy.
- Specialist referral is also recommended for paediatric patients in whom the diagnosis is uncertain, the eczema is severe with frequent flares and/or is not responding to appropriate treatment, facial atopic eczema is present and not responding to appropriate topical therapy, there is severe psychosocial impact, the family needs guidance and support for management of the child's eczema, and for patients where employment is at risk.
- Patients should also be referred to a specialist if oral steroids are required on a regular basis (more than two courses yearly) or if large amounts of topical steroids are being required and the patient is not compliant with ancillary measures (medicated baths, emollients).

### When should tar or other additives be added?

Adding tar to steroid creams increases the efficacy of the steroid without having to resort to using a stronger product. This is particularly helpful in locations such as the genital area where strong steroids are contraindicated. Tar is also useful in lichenified eczema or difficult-to-treat areas such as the hands and feet. Tar is a messy product and patients need to be made aware of this. Salicylic acid is useful as a descaling agent in hyperkeratotic eczema and menthol can be a useful addition to act as a counterirritant - some patients find the slight sting of menthol preferable to itch.

Mixing additives to steroid creams will incur a cost, which can be considerable. Generally, the use of additives is better left to specialist dermatologists with experience individualising creams for very specific purposes and patients.

### When should oral antihistamines be prescribed?

Oral antihistamines can be invaluable in managing itchy patients. Eczema has been described as "an itch that rashes". Scratching exacerbates the eczema, making the condition more likely to become chronic as well as leading to infection. Nocturnal scratching is a significant problem as it disturbs sleep for the patient as well as other household members. Non-sedating antihistamines during the day are helpful, but probably the sedating antihistamines at night are the most beneficial. The sedative effect aids deeper sleep, so scratching is less likely to occur. Many patients state that they start to itch before the rash appears and if they could only stop the scratching they would not have any rash.

### Should allergy tests be undertaken and which ones?

Patients always hope there is an easy answer to finding a single cause of their eczema and fail to understand that it is usually a multifactorial condition. They pin their hopes on finding an explanation in a single dietary or environmental allergen and they do need to understand that this is rarely the case. Some children, in particular, are put on very odd exclusion diets by their well-intentioned parents. I think it can help to arrange screening IgE and RAST tests which may find dietary allergens to be avoided, but may also reassure parents that their children can be allowed to eat a wide variety of foods without making their diets too restrictive. There is also not a complete correlation between the results of the tests and what happens in real life when the person actually consumes the food. There are limited numbers of foods which can be tested and tests are not uniformly available in NZ. I think IgE and RAST tests are indicated when there is a strong suggestion of a dietary trigger or when the patient is not responding and continues to have severe disease despite optimal management and compliance.

Prick testing can be useful in patients who seem to react in certain environments or in a seasonal pattern. I sometimes do these in families contemplating acquiring a cat or dog when there is an atopic child - it is easier to get goldfish in the first place than part with the family cat if it turns out to be an eczema trigger. Routine prick tests only measure response to a few allergens. More extensive testing is available in some centres, but this may only be possible privately and is costly. Patch testing is indicated if it seems likely there is a contact allergen, but this is of little benefit in the majority of atopic individuals. Patch tests can be very expensive and may not be available with public funding.

### When should alternative therapy such as immunosuppressants be considered?

The decision to start alternative therapies such as immunosuppressants (including cyclosporin, methotrexate, azathioprine) should not be taken lightly. These are all drugs associated with potential significant side effects, but they can be highly effective. It should be emphasised that these are only part of a management plan and do not replace the need for emollients and other topical therapies. They are almost never first-line therapy. With increasing awareness of these products there can be pressure from some patients who view them as an easy option. Patients who may benefit from these medications should be referred to specialists familiar with their use. These types of drugs should probably only be initiated by specialist dermatologists to ensure they are used appropriately and adequately monitored.

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