Summary

Topical corticosteroids have shown either high efficacy combined with poor tolerance or low efficacy combined with good tolerance. Due to its high efficacy and excellent local and systemic tolerance, Advantan offers for optimal equilibrium of efficacy and tolerance.

Advantan has been developed for the treatment of eczema, the most common indication in dermatology affecting up to 18% of the population and accounting for up to one third of medical consultations in dermatology clinics. Advantan is highly effective in all kinds of eczema, including atopic dermatitis, with a success rate (complete healing and distinct improvement) of about 90%.

The high lipophilicity of Advantan and the fact that it is bioactivated in the skin enables single daily application without any loss of efficacy. Furthermore, Advantan does not lead to any suppression of endogenous cortisol production and is therefore have minimum side effects. Thus, children can be treated with Advantan, and it is also suitable for long-term therapy in chronic forms of eczema (up to 4 weeks in children, up to 12 weeks in adults). Advantan is available in milk, cream, ointment, fatty ointment and solution forms, which is used for different skin types.

Composition

1 g Advantan® contains 1 mg (0.1 %) methylprednisolone aceponate. The cream contains benzyl alcohol 1% (w/w) as preservative.

Dosage form

(1) **Advantan® Milk – low fat/high water content (water content 67.5%)**
   It contains 0.1% MPA. The milk formulation is easy to spread over large areas. It has a useful cooling effect due to the high water content. It can be used for the treatment of mild to moderate, acute and weeping eczema. It can also be used to treat sunburn.

(2) **Advantan® Cream - low fat/high water content (water content 60%)**
   It contains 0.1% MPA. It is a white opaque cream. It is a moisturizing and easy-to-spread preparation for subacute and weeping stages of eczema.

(3) **Advantan® Ointment - balanced fat/water content (water content 30%)**
   It contains 0.1% MPA. It is a white to yellowish-white opaque ointment. It is for skin conditions that are neither weeping nor very dry. It is suitable for subacute and chronic eczema.

(4) **Advantan® Fatty Ointment – water-free lipogel**
   It contains 0.1% MPA. It is a white to yellowish translucent fatty ointment. It is for skin diseases requiring an anhydrous base, such as chronic eczema. The occlusive effect promotes healing. It is suitable for very dry skin conditions.

(5) **Advantan® Solution**
   It contains 0.1% MPA. It is a viscous solution suitable for the treatment of hairy parts of the body.
Therapeutic indications

Advantan® suppresses inflammatory and allergic skin reactions as well as reactions associated with increased cellular regeneration, leading to regression of the objective symptoms (erythema, oedema, thickening of the skin, coarsening of the skin surface) and the subjective complaints (itching, burning, pain).

Advantan® is approved for use in Atopic dermatitis (endogenous eczema, neurodermatitis), contact eczema, degenerative, dyshidrotic, vulgar eczema, eczema in children.

Pharmacological data

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).

The systemic effect of this drug is minimal in both man and animals. Methylprednisolone aceponate itself binds to the intracellular glucocorticoid receptor and this is especially true of the principal metabolite, 6α-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.

First, it induces the macrocortin synthesis which inhibits the release of arachidonic acid and thus the formation of inflammation mediators to achieve the anti-inflammatory effect. Second, it inhibits the chemotaxis and antimitotic effects in order to cause immunosuppression. Lastly, it inhibits the synthesis of vasodilating prostaglandins or potentiation of the vasoconstrictive effect of adrenaline finally result in the vasoconstrictive activity of glucocorticoid.

Bioavailability/Pharmacokinetics

Absorption

Methylprednisolone aceponate (MPA) - A special molecule

The molecular structure of Advantan® offers high intrinsic activity. The absence of halogenation does not compromise its strength but enhances safety. Double esterification increases lipophilicity and leads to a better penetration into the stratum corneum producing higher concentrations in the inflamed tissue (see table).
Monograph of Advantan®

The lipophilicity of Advantan®

<table>
<thead>
<tr>
<th>Compound</th>
<th>Koc *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>5</td>
</tr>
<tr>
<td>Hydrocortisone 21-acetate</td>
<td>15</td>
</tr>
<tr>
<td>Hydrocortisone 17-butyrate</td>
<td>160</td>
</tr>
<tr>
<td>Methylprednisolone aceponate</td>
<td>2500</td>
</tr>
</tbody>
</table>

* Koc = octanol/water partition coefficient

Distribution

Only skin area. Once it reaches the circulation, it is metabolized and eliminated.

Metabolism

MPA is hydrolysed to the principal metabolite methylprednisolone 17-propionate (MPP) by esterases in the skin (MPP has an intracellular corticoid receptor binding affinity 2.4-times that of the parent compound MPA). This bioactivation is accelerated in damaged and inflamed skin compared to normal skin. After reaching the circulatory system, the primary hydrolysis product of methylprednisolone aceponate - MPP - is rapidly conjugated with glucuronic acid and inactivated.

Elimination

After inactivation, MPA is eliminated by kidney.

Known Adverse Effects/Toxicities

(1) In 8-week comparative study comparing Advantan and betamethasone 17-valerate (BMV), it showed that BMV twice daily produces a higher incidence of and more significant (p < 0.0034) telangiectasia and skin thinning than Advantan cream once daily.

(2) In a comparative study, after 7 weeks of occlusive exposure of Advantan, clobetasol propionate (CPB) and BMV, the atrophogenic potential of CPB is highly greater than Advantan and BMV. Though there is no significant difference between Advantan and BMV, the atrophenic potential of Advantan is low.

(3) Local symptoms such as atrophy of the skin, telangiectasia, striae, acneiform changes of the skin and systemic effects of the corticoid due to absorption may occur when topical preparations containing corticoids are applied to large areas of the body (about 10% and more) or for prolonged periods of time (more than 4 weeks). However, during the clinical investigation, none of these side effects occurred on Advantan treatment up to 12 weeks (adults) and 4 weeks (children).

(4) It is suggested that Advantan has a lower incidence of skin atrophy and can be used for a long time of treatment. The lower incidence of adverse effects may due to quick inactivation during circulation.

Contraindications

Tuberculous or syphilitic processes in the area to be treated; virus diseases (e.g. varicella, herpes zoster), rosacea, perioral dermatitis and postvaccination skin reactions in the area to be treated.
Hypersensitivity to the active substance or to any of the excipients

Special Precautions

If the skin dries out excessively under protracted use of Advantan® cream, a switch should be made to one of the formulations with a higher fat content (Advantan® ointment or Advantan® fatty ointment). Advantan® should not be allowed to come in contact with the eyes when being applied to the face. No impairment of adrenocortical function has been observed either in adults or in children on large-area (40 - 60 % of the skin surface) or even occlusive treatment with Advantan®. Nevertheless, the duration of use should be kept as brief as possible when treating large areas. Advantan® should not be used continuously in adults for up to 12 weeks and in children for up to 4 weeks. As known from systemic corticoids, glaucoma may also develop from using local corticoids (e.g. after large-dosed or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin around the eyes) If a secondary microbial skin infection is present suitable concomitant antimicrobial therapy should be instituted. If fungal infections are present, a topically active antimycotic should be applied. Advantan should be used with caution in nursing mothers. 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. The treatment of psoriasis with potent topical corticosteroids may provoke the pustular form of the disease. Advantan should not be applied to skin crease areas.

Drug Interaction

No specific information exists on interactions with other medications.

Evidence-based clinical guideline

During the last five years better possibilities have appeared for investigation and medical treatment of dementia. Society and the national health authorities have a growing demand for systematical identification of dementia. In 1999, DSAM published a clinical guideline for identifying dementia.

Clinical study

Advantan cream and ointment were studied for their clinical efficacy and tolerance in 6 multicentre studies involving 1723 patients with different forms of eczema.

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Cream studies</th>
<th>Ointment studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Contact dermatitis</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>2. Irritant eczema</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>3. Non-classifiable eczema</td>
<td>395</td>
<td>358</td>
</tr>
<tr>
<td>4. Nummular eczema</td>
<td>137</td>
<td>132</td>
</tr>
<tr>
<td>5. Pompomlyx</td>
<td>149</td>
<td>95</td>
</tr>
<tr>
<td>6. Selbhoroeic eczema</td>
<td>109</td>
<td>74</td>
</tr>
</tbody>
</table>

| Total                         | 875           | 848              |

Patients were treated either with methylprednisolone aceponate (MPA) or betamethasone 17-valerate (BMV) cream (875) or ointment formulations (848), in accordance with basic principles as decided by the attending physician: MPA 2x/day (564 patients); MPA1x/day plus vehicle 1x/day (581 patients); BMV 2x/day (578 patients). Patients were randomly assigned to MPA or BMV; thus,
1145 patients received MPA (568 cream and 559 ointment formulations) and 578 BMV (cream formulation).

Therapeutic success (healing or distinct improvement) was achieved within weeks in a total of 91% of the patients treated with Advantan (1038 of 1145 cases).

Advantan cream and ointment (once-daily plus vehicle) were compared with the potent corticosteroid betamethasone 17-valerate (BMV) in a twice-daily application in 2 clinical studies conducted as a multicentre group comparison. As shows above, 92.3% of patients treated with Advantan and 95.5% of those treated with BMV were graded as healed or distinctly improved. No differences were demonstrable between the treatment groups. Advantan ointment once-daily (plus vehicle) was compared with hydrocortisone 17-butyrate (HCB) fatty cream twice daily in 40 patients (group comparison with 20 patients each) with different kinds of eczema. After completion of therapy (treatment up to 4 weeks), Advantan displayed higher efficacy that was statistically significant (healing 70%, distinct improvement 30%) in comparison to HCB fatty cream (healing 20%, distinct improvement 50%, slight improvement 30%). Local side effects did not occur.

Cost comparison

Eczema is commonly treated with topical corticosteroid. Some contain corticosteroid alone or in combination with other agents useful in eczema. The table below summarized Advantan cream in comparison with some other preparations containing single corticosteroid as active ingredient available in hospital.
### Monograph of Advantan®

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Pack size</th>
<th>Cost ($)#</th>
<th>Dosing</th>
<th>Cost/treatment* ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantan®</td>
<td>Methylprednisolone aceponate 0.1%</td>
<td>10g cream</td>
<td>38</td>
<td>qd</td>
<td>26.6</td>
</tr>
<tr>
<td>Berthnovate®</td>
<td>Betamethasone valerate 0.1%</td>
<td>15g cream/15g ointment</td>
<td>10.4/910.22</td>
<td>bid-tds</td>
<td>9.7-14.6</td>
</tr>
<tr>
<td>Synalar®</td>
<td>Fluocinolone acetonide 0.005%</td>
<td>5g cream</td>
<td>3.49</td>
<td>qd-tds</td>
<td>4.9-14.7</td>
</tr>
<tr>
<td>Synalar®</td>
<td>Fluocinolone acetonide 0.025%</td>
<td>5g cream</td>
<td>3.55</td>
<td>qd-tds</td>
<td>4.9-14.7</td>
</tr>
<tr>
<td>Nerisone®</td>
<td>Diflucortolone valerate 0.1%</td>
<td>15g cream/15g ointment</td>
<td>24/33.73</td>
<td>bid-tds</td>
<td>22.4-33.6</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 1%</td>
<td>5g cream</td>
<td>1.68</td>
<td>bid</td>
<td>4.7</td>
</tr>
</tbody>
</table>

# Cost for Advantan cream from HKIMS, others from drug formulary from HA hospital.
* Assume a 7-day course of treatment, each dose required 1 g.

### References


