Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Advantan cream 0.1% w/w

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Also contains Cetostearyl Alcohol and Butylhydroxytoluene (E321)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
Oil in water emulsion, white to yellowish opaque cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Topical treatment of corticosteroid sensitive dermatoses.

4.2 Posology and method of administration

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.

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).

Pediatric population
Dose adjustments are not required when Advantan cream is administered to children aged 3 years or older and adolescents. In general, the duration of use should not exceed 4 weeks in children.

The safety of Advantan Cream in infants below the age of 4 months has not been established.

4.3 Contraindications

Known hypersensitivity to the active ingredients or any of its excipients

Primary bacterial, viral and fungal diseases of the skin and secondarily infected eczemas or intertrigo acne, perioral dermatitis, rosacea atrophic skin diseases and vaccination skin reactions in the area to be treated and, in general, should not be used on weeping surfaces.

4.4 Special warnings and precautions for use

Glucocorticoids must only be used at as low a dose as possible, especially in children, and only for as long as is absolutely necessary to achieve and maintain the desired therapeutic effect.
Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate therapy.
Local skin infections can be potentiated by topical glucocorticoid use.
Care must be taken when using Advantan to avoid contact with the eyes, deep open wounds and mucosae. Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes

which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.
No impairment of adrenocortical function has been observed in children on large-area (40 - 90 % of the skin surface) non-occlusive treatment with Advantan 0.1% fatty ointment. After application of Advantan 0.1% ointment to 60 % skin surface area under occlusive conditions for 22 hours, suppression of plasma cortisol levels and influence on circadian rhythm was observed in adult healthy volunteers.
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. Treatment under occlusive conditions should be avoided unless indicated. Note that diapers/nappies as well as intertriginous areas might represent occlusive conditions.
When treating large areas of skin, the duration of treatment should be kept as short as possible as the possibility of absorption or a systemic effect cannot be completely excluded.
As with all other glucocorticoids unprofessional use can mask clinical symptomatology.
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).
This product contains butyl hydroxytoluene (E321) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes, and cetylstearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).
The excipient (hard fat) in Advantan Cream may reduce the effectiveness of latex products such as condoms and diaphragms.
This medicine contains 1.0 g benzyl alcohol in each 100 g. Benzyl alcohol may cause allergic reactions and/or mild local irritation.

Paediatric Population
MPA should not be used under occlusive conditions. Note that diapers can be occlusive.
A careful benefit/risk assessment is needed in the case of children between 4 months and 3 years.

4.5 Interaction with other medicinal products and other forms of interactions

None so far known.

4.6 Fertility, pregnancy and lactation

4.6.1 Fertility

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

4.6.2. Pregnancy
There are no adequate data from the use of Advantan cream, ointment and fatty ointment in pregnant women.
Animal experimental studies with glucocorticosteroids have shown reproductive toxicity (see section "5.3 Preclinical safety data).
A number of epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with systemic glucocorticosteroids 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 women.

In general, the use of topical preparations containing corticoids should be avoided during the first trimester of pregnancy. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during pregnancy.

4.6.3 Lactation
In rats methylprednisolone aceponate showed practically no transfer to the neonates via the milk.But it is not known if methylprednisolone aceponate is secreted in human milk as systemically administered corticosteroids have been reported to appear in human milk.It is not known whether topical administration of Advantan cream, ointment and fatty ointment could result in sufficient systemic absorption of methylprednisolone aceponate to produce detectable quantities in human milk. Therefore caution should be exercised when Advantan cream, ointment and fatty ointment are administered to a nursing woman.
Nursing mothers should not be treated on the breasts. Treating large areas, prolonged use or occlusive dressings should be avoided during lactation (see section 4.4).

4.7 Effects on ability to drive and use machines

Advantan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies, most frequently observed side-effects included application site burning and application site pruritus with Advantan cream and ointment. For Advantan fatty ointment, application site folliculitis and application site burning were observed most frequently.

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.

System organ class	**Common**	**Uncommon**	**Rare**	**Frequency not known***
General disorders and administration site reaction	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 edema, application site irritation	hypertrichosis
Immune system disorders		drug hypersensitivity		
Infections and infestations			fungal skin infection	
Skin and subcutaneous tissue disorders			pyoderma, skin fissures, telangiectasia, skin atrophy, acne	skin striae, perioral dermatitis, skin discolouration, allergic skin reaction
Eye disorders				Blurred vision (see section 4.4)

* Potential undesirable effects not observed in clinical studies.

The most appropriate MedDRA term (MedDRA version 11.1) was used to describe a certain reaction and its synonyms and related conditions.
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 and allergic skin reactions to one of the ingredients of the formulations. Systemic effects due to absorption may occur when topical preparations containing corticoids are applied.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie E-mail: medsafety@hpra.ie.

4.9 Overdose

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 favorable to absorption) or inadvertent oral ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: corticosteroids, potent (group III), ATC code: D07AC14
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).

It is known that methylprednisolone aceponate itself binds to the intracellular glucocorticoid receptor and this is especially true of the principal metabolite 6 alpha-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.

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 adrenaline finally result in the vasoconstrictive activity of glucocorticoids.

5.2 Pharmacokinetic properties

Methylprednisolone aceponate becomes available in the skin from the formulation base. 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 than the parent drug, an indication of bioactivation in the skin.

The rate and extent of percutaneous absorption of a topical corticoid depends on a series of factors: chemical structure of the compound, the composition of the vehicle, the concentration of the compound in the vehicle, the conditions of exposure (area treated, duration of exposure, open or occlusion) and the skin status (kind and severity of skin disease, anatomical site etc.). Percutaneous absorption of methylprednisolone aceponate from the cream, ointmentand fatty ointmentformulations has been investigated in healthy volunteers. The percutaneous absorption after open application of the Advantan fatty ointment (2 x 20 g daily) for 5 days was estimated to 0.34 % corresponding to a corticoid load of approximately 2 µg/kg/day. The respective figures after open application of the Advantan ointment (2 x 20 g daily) for 8 days were 0.65 % (absorption) or 4 µg/kg/day (load). Under occlusive conditions the daily application of 2 x 20 g Advantan cream for 8 days led to a mean percutaneous absorption of ca. 3 % corresponding to a systemic corticoid load of ca. 20 µg/kg/day. The percutaneous absorption of methylprednisolone aceponate through skin pre-damaged by removal of the stratum corneum resulted in distinctly higher absorption (13-27 % of the dose). In adult psoriatic and atopic patients, percutaneous absorption of methylprednisolone aceponate from the fatty ointment was about 2.5%. In three atopic children (9-10 years of age), percutaneous absorption of methylprednisolone aceponate from the fatty ointment was about 0.5-2%and thus not higher than that compared to adults. After reaching the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, 6 alpha-methylprednisolone-17-propionate, is quickly conjugated with glucuronic acid and inactivated as a result.

The metabolites of methylprednisolone aceponate (main metabolite: 6 alpha-methylprednisolone-17-propionate-21-glucuronide) are eliminated primarily via the kidneys with a half-life of about 16 hours. Following i.v. administration, excretion of the ^{14}C-labelled substances with the urine and faeces was completed 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 methylprednisolone aceponate showed the action profile of a typical glucocorticoid. It can be concluded from these results that following therapeutic use of Advantan cream, ointment and fatty ointment no side-effects other than those typical of glucocorticoids are to be expected even under extreme conditions such as application over a large surface and/or occlusion.

Embryotoxicity studies with Advantan led to results typical for glucocorticoids, i.e. embryolethal and/or teratogenic effects are induced in the appropriate test system.

In view of these findings, particular care should be taken when prescribing Advantan during pregnancy. The results of epidemiological studies are summarized under section "4.6 Pregnancy and lactation".

Neither in vitro investigations for detection of gene mutations on bacteria and mammalian cells nor in vitro and in vivo investigations for detection of chromosome and gene mutations gave any indication of a genotoxic potential of methylprednisolone aceponate.
Specific tumorigenicity studies using methylprednisolone aceponate have not been carried out. Knowledge concerning the structure, the pharmacological effect mechanism and the results from systemic tolerance studies with long-term administration do not indicate any increase in the risk of tumor occurrence.As systemically effective immunosuppressive exposure is not reached with dermal application of Advantan cream, ointment and fatty ointment under the recommended conditions of use, no influence on the occurrence of tumors is to be expected.

In investigations of local tolerance of methylprednisolone aceponate and Advantan formulaions on the skin and the mucosa, no findings other than the topical side effects known for glucocorticoids were recorded.

Methylprednisolone aceponate showed no sensitising potential on the skin of a guinea-pig.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Decyl Oleate
Glycerol monostearate (40-55)
Cetolstearyl Alcohol
Hard fat
Glycerol fatty acid tri-esters (Softisan 378)
Polyoxyl-40-stearate
Glycerol 85% (E422)
Disodium edetate
Benzyl alcohol
Butylhydroxytoluene (E321)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Tubes with 5, 10, 15, 30, 50 or 100 g.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1025/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:3rd April 1998
Date of last renewal: 3rd April 2008

10 DATE OF REVISION OF THE TEXT

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