Bayer HealthCare

Summary of Product Characteristics

Advantan*

Methylprednisoloneaceponate

0.1%Cream

* This medicinal product is registered / marketed under the following trade names: Advantan, Adventan, Avancort or Lexxema.

1. NAMEOFTHEMEDICINALPRODUCT

Advantan 0.1%cream

2. QUALITATIVE ANDQUANTITATIVE COMPOSITION IN TERMS OF THEACTIVE SUBSTANCE(S)

1 gAdvantan creamcontains 1 mgmethylprednisolone aceponate (0.1 %)

Fora full list of excipients, seesection 6.1.

3. PHARMACEUTICALFORM

Cream (whiteto yellowish opaque cream)

4. CLINICALPARTICULARS

4.1 Indications

Acute inflammatory skin diseases in adults and children above 4 months of age:
endogenous eczema (atopic dermatitis, neurodermitis), contact eczema, degenerative eczema, dyshidrotic eczema, eczema in children.

4.2 Dosageandmethodofadministration

Medicinal product is applied thinly once per day to the diseased areas of skin.
Duration of Advantan cream use should not exceed 12 weeks in adults.

Pediatricpopulation

Advantan is administered in children above 4 months of age. Dose adjustments are not required. The duration of use should be minimal and should not exceed 4 weeks.

4.3 Contraindications

Tuberculousorsyphiliticprocessesintheareatobetreated;viraldiseases (e.g. varicella, herpeszoster),rosacea,perioraldermatitis,ulcers,acnevulgaris,atrophicskindiseases and postvaccination skin reactions in the areato betreated.
Hypersensitivityto the activesubstanceorto anyofthe excipients.

4.4Special warnings and precautions foruse

Additional,specifictherapyisrequiredinbacterially infectedskindiseasesand/orin fungal infections.
Iftheskindriesoutexcessively underprotracteduseofAdvantancream,aswitchshould bemadetooneof the formulationswitha higher fatcontent(Advantanointmentor Advantan fattyointment).
CaremustbetakenwhenusingAdvantancream toavoid contact with the eyes,deep open woundsand mucosae.

11.12.2016

AfterapplicationofAdvantanto60%skinsurfaceareaunder occlusive conditionsfor 22hours,suppressionof plasma cortisollevelsandinfluence on circadian rhythm was observed in adult healthyvolunteers.
Extensiveapplicationoftopicalcorticosteroidstolargeareasofthebodyor forprolonged periodsoftime,inparticularunderocclusion,significantly increasestheriskofsystemic side effects. Notethat diapers can beocclusive.
Asknownfromsystemiccorticoids,glaucomamay alsodevelopfromusinglocal corticoids(e.g.afterlarge-dosedorextensiveapplicationover a prolongedperiod, occlusivedressingtechniques, or application to theskin around the eyes).
TwoexicipientscontainedinAdvantan0.1%cream(cetostearylalcohol and butyl hydroxytoluene)may causelocalskinreactions(e.g.,contactdermatitis).Butyl hydroxytoluenemayalso causeirritation in the eyes and mucous membranes.

4.5 Interactionwithothermedicinal products andotherforms ofinteraction

Noneso farknown.

4.6 Pregnancy andlactation

4.6.1 Pregnancy

There areno adequatedata from theuseofAdvantan cream in pregnant women.
Animal experimental studies withmethylprednisolone aceponate have shown embryotoxicand/orteratogeniceffects(seesection"5.3Preclinicalsafety data").In general,theuseoftopicalpreparationscontaining corticoidsshouldbe avoided duringthe firsttrimesterofpregnancy.Inparticular,treating largeareas,prolongeduseorocclusive dressings should be avoided duringpregnancy.
Epidemiologicalstudiessuggestthattherecouldpossiblybeanincreasedriskoforal cleftsamongnewbornsofwomenwhoweretreatedwithglucocorticosteroidsduring the first trimesterofpregnancy.
TheclinicalindicationfortreatmentwithAdvantancreammustbecarefully reviewedand thebenefits weighed against the risks in pregnant women.

4.6.2 Lactation

Inratsmethylprednisoloneaceponateshowedpracticallynotransfertotheneonatesvia themilk.Butitisnotknownifmethylprednisoloneaceponateis secreted in human milk as systemicallyadministered corticosteroids have beenreported to appear inhuman milk.Itisnotknownwhethertopicaladministrationof Advantancreamcouldresultin sufficientsystemicabsorptionofmethylprednisoloneaceponatetoproduce detectable quantitiesinhumanmilk.Therefore cautionshouldbe exercisedwhenAdvantancreamis administered to anursingwoman.
Nursing mothersshouldnotbetreatedonthebreasts.Treating largeareas, prolonged use orocclusivedressings should be avoided duringlactation.

4.7 Effects onability to driveorusemachines

Advantan cream has no influenceon the abilityto drive and usemachines.

11.12.2015

4.8 Undesirable effects

Inclinicalstudies,mostfrequentlyobservedside-effectsincludedapplicationsiteburning andapplicationsiteprurituswithAdvantancrcam.

Frequenciesofside-effectsobservedinclinicalstudiesandgiveninthe table below are definedaccording to the MedDRAfrequency convention: very common (>1/10); common(>1/100,<1/10);uncommon(>1/1,000;<1/100),rare(>1/10,000,<1/1,000); veryrare(<1/10,000),notknown(cannot be estimated from the availabledata). MedDRA version 12.0 was used for coding.

Systemorganclass	common	uncommon	rare
General disorders and administrationsite reaction	application site burning, application site pruritus	application site dryness, application site erythema, application site vesicles, application site folliculitis, application site rash, application	application site cellulitis, application site edema, application siteirritation
Immunesystem disorders		drug hypersensitivity	
Skinandsubcutaneous tissuedisorders			pyoderma, skin fissures, telangiectasia, skin atrophy, fungal skin infection, acne

Aswithothercorticoidsfortopicalapplication,thefollowinglocalsideeffectsmay occur:skinatrophy,skinstriae,applicationsitefolliculitis, hypertrichosis, telangiectasia, perioraldermatitis,skindiscoloration,andallergicskinreactionstoanyoftheingredients oftheformulations.Systemiceffectsduetoabsorptionmay occurwhentopical preparations containingcorticoids are applied.

4.9 Overdose

Resultsfromacutetoxicity studiesdonotindicatethatany riskofacuteintoxicationisto beexpectedfollowing asingledermal application of an overdose (application overalarge areaunder conditions favorableto absorption)orinadvertent oral ingestion.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamicproperties

Pharmacotherapeuticgroup: corticosteroids, potent (group III), ATCcode: D07AC14.

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Aftertopicalapplication,Advantancreamsuppressesinflammatory andallergicskin reactionsaswellasreactionsassociatedwithhyperproliferation,leading toregressionof theobjectivesymptoms(erythema,edema,weeping) andthe subjective complaints (itching, smarting, pain).
Itisknownthatmethylprednisoloneaceponateitselfbindstothe intracellular glucocorticoidreceptorandthisisespecially trueforthepricipalmetabolite6α-methylprednisolone-17-propionate, which is formed after cleavageofthe esterin theskin.
Thesteroidreceptorcomplexbindstocertainregionsof DNA,thereby triggeringaseries ofbiological effects.
Bindingof the steroidreceptor complexresultsininductionof macrocortinsynthesis.Macrocortininhibitsthereleaseofarachidonicacidandthusthe formationof inflammatorymediators such as prostaglandins and leukotrienes.
Theimmunosuppressiveactionofglucocorticoidscanbeexplainedby inhibitionof cytokinesynthesis and an antimitotic effect, which so faris not well understood.
Inhibitionofthesynthesisofvasodilating prostaglandinsorpotentiationofthe vasoconstrictiveeffectofadrenalinefinally resultsinthevasoconstrictiveactivity of glucocorticosteroids.

5.2 Pharmacokineticproperties

Methylprednisolone aceponate becomes available from the formulation base. The concentration in the stratum corneum and living skin decreases from the outside to the inside. Methylprednisolone aceponate is hydrolized in the epidermis and dermis to the main metabolite 6α-methylprednisolone-17-propionate which binds more firmly to the corticoid receptor than the parent drug, an indication of a 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 formulations has been investigated in healthy volunteers. The respective figures after open application of the Advantan cream (2 x 20 g daily) for 8 days were 0.65 % (absorption) or 4 µg/kg/day (load). 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).
After reaching the systemic circulation, the primary hydrolysis product of methylprednisolone aceponate, 6α-methyl-prednisolone-17-propionate is quickly conjugated with glucuronic acid and as a result, inactivated.The metabolites of methylprednisolone aceponate (main metabolite: 6α-methyl prednisolone-17-propionate-21-glucuronide) are eliminated primarily via the kidneys with a half-life of about 16 hours. Following i.v. administration, excretion with the urine and feces was complete within7 days.Noaccumulationofdrugsubstanceormetabolites takes placein thebody.

5.3 Preclinical safety data

Insystemictolerancestudiesfollowing repeatedsubcutaneousanddermaladministration methylprednisoloneaceponateshowedtheactionprofileofatypical glucocorticoid. It can beconcludedfromtheseresultsthatfollowing therapeuticuseofAdvantancreamno side-effectsotherthanthosetypicalofglucocorticoidsaretobe expectedevenunder extreme conditions such as application overalargesurface and/orocclusion.

11.12.2011

Embryotoxicity studies with Advantan cream 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 cream during pregnancy.
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 under the recommended conditions of use, no influence on the occurrence of tumors is to be expected.
In investigations of the local tolerance of methylprednisolone aceponate and Advantan formulations on the skin and the mucosa no findings other than the topical side-effects known for glucocorticoids were recorded.
Methylprednisolone aceponate showed no sensitizing potential on the skin of the guinea- pig.

6. PHARMACEUTICALPARTICULARS

6.1 Listofexcipients

Decyl oleate
Glycerol monostearate40 – 55 %
Cetostearyl alcohol
Hard fat
Caprylic-capric-myristic-stearictriglyceride (Softisan 378)
Macrogol stearate40
Glycerol (85 %)
Disodium edetate
Benzyl alcohol
Butyl hydroxytoluene
Water, purified

6.2 Incompatibilities

Not applicable

6.3 Shelflife

3 years

6.4 Special precautions forstorage

Do not store above 25 °C. Keep out of reach of children.

6.5 Natureandcontents ofcontainer

Tubesmadeofpurealuminium,interiorwallcoatedwithepoxyresin,andwithpolyester-basedexternalcoating;endsealband.The screwcapismade ofhighdensity polyethylene.
Presentation: 15-g.

6.6 Instructions foruse/ handling

No special requirements

7. MAH NAME AND ADDRESS

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