15 June 2022
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Cortaderm (EMEA/V/C/005579/0000)

INN: hydrocortisone aceponate

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

The applicant Curados B.V. submitted on 26 November 2020 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Cortaderm through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic). During the procedure the MAH was transferred from Curados B.V. to Alfasan Nederland B.V.

The eligibility to the centralised procedure was agreed upon by the EMA/CVMP on 20 February 2020 as the product would constitute a generic product of a product authorised through the centralised procedure, Cortavance (reference product).

At the time of submission, the applicant applied for the following indication for the target species dog: for symptomatic treatment of inflammatory and pruritic dermatoses.

As per the latest variation of the reference product Cortavance the following indication has been added to the application of Cortaderm: For alleviation of clinical signs associated with atopic dermatitis.

Cortaderm contains one active substance - hydrocortisone aceponate. Hydrocortisone aceponate belongs to the diesters class of the glucocorticosteroids. The diesters are lipophilic components ensuring an enhanced penetration into the skin associated to a low plasma availability. Hydrocortisone aceponate thus accumulates in the dog's skin allowing local efficacy at low dosage. The diesters are transformed inside the skin structures. This transformation is responsible for the potency of the therapeutic class.

Cortaderm cutaneous spray solution contains 0.584 mg/ml hydrocortisone aceponate and is presented in packs containing 1 bottle.

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Niels Christian Kyvsgaard and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 13(3) of Directive 2001/82/EC – a hybrid application.

On 15 June 2022, the CVMP adopted an opinion and CVMP assessment report.

On 27 July 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for Cortaderm.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a new detailed description of the pharmacovigilance system (version 4.3

dated June 2013) due to the change in the MAH to Alfasan Nederland B.V. which fulfils the requirements of Directive 2001/82/EC. Based on the information provided, the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Batch release is performed at the following manufacturing site: Produlab Pharma B.V., Raamsdonksveer, The Netherlands.

The manufacturing authorisation for Produlab Pharma B.V. was issued on 15 September 2020 by the Medicines Evaluations Board, The Netherlands. GMP certification confirms the date of the last inspection (11 March 2020) and shows that the site is appropriately authorised for batch release.

A QP declaration is provided by the finished product manufacturer and is acceptable.

All sites involved in the manufacture of the veterinary medicinal product have been demonstrated to operate in accordance with the required EU GMP standards.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements. The submitted DDPS has already been approved by Member States during previous MR/DC/Centralised procedures.

The GMP status of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements. An on-site audit will be performed on 12 July 2022 for the active substance manufacturing site. However, the QP declaration based on the remote assessment is acceptable.

Part 2 - Quality

Composition

The finished product is presented as a cutaneous spray solution containing 0.584 mg/ml of hydrocortisone aceponate as active substance.

A single excipient propylene glycol methyl ether (PGME) is used, as described in section 6.1 of SPC.

The product is available in a HDPE, 10 ml, container with a screw cap and an enclosed spray pump, as described in section 6.5 of the SPC.

Containers

The primary packaging is white, high-density polyethylene, 10 mL round spray bottle closed with a tamper evident, child resistant, white polypropylene screw cap. The bottle is supplied with a spray pump, which should be screwed on the bottle prior to administration. Each bottle is packed into a cardboard box. The pack size of 10 ml is sufficient to treat a reasonable sized dog for 7 days.

The packaging material, including the outer layer of the screw cap liner (polytetrafluorethylene) complies with the relevant European Pharmacopoeia (Ph. Eur.) requirements and EU Regulation 10/2011 on plastic materials and articles intended to come into contact with food.

The compatibility of the HDPE bottle with PP cap with the medicinal product was evaluated with an extraction study. The extractables were deemed to be typical for polyethylene and it has been

demonstrated that the extractables are below the calculated concentration limits or, when above the limit, are toxicologically safe at the level found. The bottle including cap and spray pump have been included in the extraction studies. Migration studies are not required.

An extraction study was also performed on the spray pump using the same conditions and analytical methods as for the HDPE bottle with screw cap. Results are presented for volatile organic impurities, semi-volatile organic impurities and non-volatile organic impurities. The extractables were deemed to be typical additives in plastic. None of the extractables were above the concentration limits.

Development of the finished product focused on the choice of container closure system and functionality of the spray pump. Dose accuracy and spray pattern has been shown similar to the reference product.

Development pharmaceutics

The finished product was developed to mimic the reference product, i.e. same type of solution, same concentration of active substance, and same excipient propylene glycol methyl ether. The excipient is a non-pharmacopoeial substance.

Batch comparison in terms of appearance, density, identification, assay, and related substances has been performed using one batch of the reference product and two batches of the test product. The physical and chemical comparison of reference and test product supports the similarity of the two products.

It has been shown that the finished product possesses inherent antimicrobial properties.

Method of manufacture

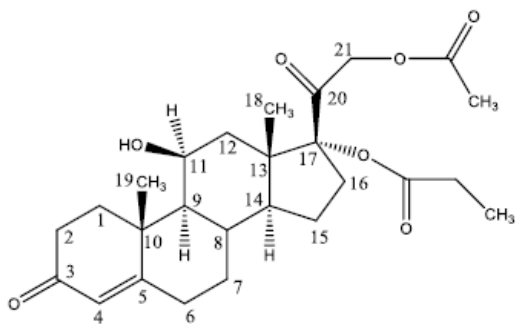
The manufacturing process consists of 2 main steps: Dissolution of the active substance in PGME and filling. The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing the finished product in a reproducible manner by the finished product manufacturer.

The manufacturing process is a standard process consisting solely of dissolution and filling steps. Sufficient details have been provided. The applicant has confirmed that the validation of the manufacturing process will be performed with the first 3 commercial batches..

Control of starting materials

Active substance



Chemical name: Hydrocortisone 21-acetate 17-propionate

Appearance:	White to slightly yellowish crystalline powder
Solubility:	Soluble in alcohol, dimethylformamide and methylethylketone. Sparingly soluble in diethyl ether. Practically insoluble in water.
Melting range:	Between 149 °C to 153 °C
Specific optical rotation:	+66.5º to +69.0º (10 mg/ml, in dioxane), calculated with reference to the anhydrous and solvent-free substance
Chirality	Hydrocortisone aceponate has 7 asymmetric carbons at: C_8, C_9, C_{10}, C_{11}, $C1_3$, C_{14} and C_{17}. The above mentioned atoms are all part of the tetradecahydrocyclopentanephenanthrene skeleton that is already present in the starting material (hydrocortisone alcohol)
Polymorphism:	See S.3.1
Particle size:	The active substance is micronized, see S.4.1 for specifications
Hygroscopicity	Not hygroscopic
Physical form	Hydrocortisone aceponate has 7 asymmetric carbons at: C8, C9, C10, C11, C13, C14 and C17. The above mentioned atoms are all part of the tetradecahydrocyclopentanephenanthrene skeleton that is already present in the starting material (hydrocortisone alcohol).

The active substance hydrocortisone aceponate is not covered by a Ph. Eur. monograph and full documentation for the active substance is presented as an ASMF.

The chemical-pharmaceutical documentation in relation to hydrocortisone aceponate is of sufficient quality in view of the present European regulatory requirements. The description of the manufacturing process is acceptable.

Impurity profile and other relevant sections of the active substance master file are satisfactorily presented and justified.

Stability studies have been performed with the active substance at accelerated and long-term storage conditions. The proposed retest period of 24 months/ at 5 °C ± 3 °C, protected from light is acceptable.

Excipients

The excipient propylene glycol methyl ether is a non-pharmacopoeial substance. The specification includes a test for the specified impurity 2-methoxy-1-propanol with a maximal limit of 0.1%.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product does not contain any materials derived from human or animal origin.

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The specification parameters proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.

Sufficient justification has been provided for the omission of control of water content and viscosity.

The analytical methods used have been adequately described and validated in accordance with the ICH guideline. Satisfactory information regarding the reference standard hydrocortisone aceponate used for assay and impurities testing has been presented.

Batch analysis results are provided for two pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data from two pilot scale batches of finished product stored under long term conditions (5 °C, under intermediate conditions (30 °C/65% RH) and under accelerated conditions (40 °C/75% RH) for 6 months and under long term conditions (25 °C/60% RH) for 24 months was provided. According to the VICH GL3 Stability testing of new veterinary drug substances and medicinal products, stability data should be presented for at least three pilot batches. The applicant has confirmed that the first three production batches (500 L) will be placed on long term stability studies through the proposed shelf life and on accelerated studies for 6 months, in line with guideline on stability testing: stability testing of existing active substances and related finished products, EMEA/CVMP/QWP/846/99-Rev.1.

The batches of Cortaderm are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, density, assay and related substances. The analytical procedures used are stability indicating and a shelf-life of 12 months is applied.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

Part 3 – Safety

The product is a solution for symptomatic treatment of inflammatory and pruritic dermatosis in dogs containing hydrocortisone aceponate as active ingredient. The reference product is the centrally authorised product Cortavance 0.584 mg/ml cutaneous spray solution for dogs. The formulation has been used in veterinary medicine for more than 10 years. Bioequivalence cannot be demonstrated through bioavailability studies and thus Article 13(3) of Directive 2001/82/EC – hybrid application, applies.

The product is intended for cutaneous administration and is of the same type of solution, contains the same amount of the active substance (0.584 mg/mL of hydrocortisone aceponate) and the same amount of the only excipient, the solvent propylene glycol methyl ether, as Cortavance. The target species, the therapeutic scheme and the indications are identical to those of the reference product. The manufacturing process is very simple and any potential differences between the manufacturing process of the test and reference product are not expected to impact the safety of Cortaderm. The delivered dose and spray pattern are also considered similar between reference and test product. On this background no toxicological tests or efficacy studies have been submitted.

It is considered that a complete safety file is not required for this topical formulation and that equivalence can be assumed through demonstration of equivalent composition and equivalent pharmaceutical properties between the candidate and the reference product. Please also refer to Part 4.

Safety documentation

The candidate and reference products can be considered equivalent and toxicological studies are not required. The toxicological aspects of this product are considered identical to those of the reference product.

The product contains the same excipient and in the same amount as the reference product. The excipient is well-known, is widely used in pharmaceutical products intended for human and veterinary use and is not considered to represent a safety concern.

User safety

No user risk assessment has been submitted. This is considered acceptable taking into account the legal basis of this application and that the candidate product is considered equivalent to the reference product (i.e. same composition, target species, therapeutic scheme and indications; furthermore, the pump spray deliverance is the same as that of the reference product). The manufacturing process is very simple and any potential differences between the manufacturing process of the test and reference product are not expected to impact the safety of Cortaderm.

The risks for the user handling this veterinary medicinal product are expected to be the same as those of the reference product. No greater hazard is anticipated and those of the reference product apply.

Environmental risk assessment

The Environmental Risk Assessment (ERA) of the pharmaceutical product was performed according to the relevant guidelines, i.e. VICH GL6 and the CVMP 'Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMEA/CVMP/ERA/418282/2005-Rev.1). The conclusion is that the ERA can stop at phase I and no phase II is required because the veterinary medicinal product will only be used in non-food

producing animals. The product is not expected to pose a risk for the environment when used according to the summary of product characteristics.

Residues documentation

Not applicable.

Overall conclusions on the safety documentation

Bioequivalence cannot be demonstrated through bioavailability studies and thus Article 13(3) of Directive 2001/82/EC – hybrid application, applies. It is considered that results of toxicological or pharmacology test are not required for this topical formulation, and that equivalence with the reference product is accepted.

The excipient used in the formulation is well known, is widely used in pharmaceutical products intended for human and veterinary use and is not considered to represent a safety concern.

An ERA phase I evaluation was provided and the product is not expected to pose a risk for the environment when used according to the summary of product characteristics.

The product contains the same amount of active substance and excipient as the reference product. The target species, the therapeutic scheme and indications are identical to those of the reference product. The manufacturing process is very simple and any potential differences between the manufacturing process of the test and reference product are not expected to impact the safety of Cortaderm. The delivered dose and spray pattern are also considered similar between reference and test product. The risks for the user handling this veterinary medicinal product are considered to be the same as those of the reference product and hence the same precautions apply.

Part 4 – Efficacy

The application qualifies as a hybrid application under Article 13(3) of Directive 2001/82/EC since bioequivalence cannot be demonstrated. The reference product is the centrally authorised product Cortavance 0.584 mg/ml cutaneous spray solution for dogs. The proposed product Cortaderm and the reference product have identical indications: i.e. symptomatic treatment of inflammatory and pruritic dermatoses and for alleviation of clinical signs associated with atopic dermatitis in the same target species (dog), and are to be administered by the same dosing regimen.

The proposed product Cortaderm is intended for cutaneous administration and is of the same type of solution, contains the same concentration of the active substance and the same excipient, as the reference product Cortavance.

Although in vivo bioequivalence cannot be determined for this topical formulation, pharmaceutical equivalence (i.e. equivalent pharmaceutical properties), can be assumed considering the equivalent composition of the candidate and the reference product. The physical and chemical comparison of reference and test product supports the similarity of the two products as explained in part II.

Both products are simple solutions of hydrocortisone aceponate in propylene glycol methyl ether with no other excipients. The manufacturing process is very simple and any potential differences between the manufacturing process of the test and reference product are not expected to impact the efficacy and target animal safety of Cortaderm.

Both candidate and reference product are supplied with a spray pump to facilitate the cutaneous administration. To be able to assume pharmaceutical equivalence, the candidate product needs to prove that the same dosage and spray pattern of the veterinary medicinal product are provided. In

part II of the assessment, it is concluded that the uniformity of mass of delivered dose was acceptable in a dose accuracy study. The two devices can be considered to provide the same amounts of product. As a result, the candidate and reference product are considered to be pharmaceutically equivalent. Accordingly, no target animal safety and efficacy studies are requested.

Pharmacodynamics/ Pharmacokinetics

No proprietary data was provided since this is an application submitted in accordance with article 13(3) of Directive 2001/82/EC. The product has the same composition and dosing regimen as the reference product. As pharmaceutical equivalence with the reference product can be accepted, the pharmacological aspects of this product are deemed to be identical to the reference product.

Target animal tolerance

No data from specific tolerance studies are presented for Cortaderm. Given the legal basis of this application and since the product contains the same amount of active substance and excipient as the reference product and equivalence with the reference product has been accepted, a similar tolerance profile for the target species is assumed.

Administration of Cortaderm in accordance with SPC recommendations is expected to be generally well-tolerated but might lead to reactions at the application site (erythema and/or pruritus) in very rare cases.

Clinical field trials

Given the nature of the application and considering that pharmaceutical equivalence has been accepted with the reference product, it is considered acceptable that no clinical efficacy studies were provided.

Overall conclusion on efficacy

Cortaderm 0.584 mg/ml cutaneous spray solution for dogs is a hybrid application submitted in accordance with Article 13(3) of Directive 2001/82/EC.

The reference product, Cortavance and the candidate product Cortaderm are both cutaneous solutions containing the same concentration of active substance and excipient and present the same physico-chemical characteristics. The delivery dose and spray pattern are similar between the two products. Since pharmaceutical equivalence is accepted, and indication and posology are identical, both the proposed and reference products are expected to have the same target animal safety and efficacy profiles for the same indications and posology.

Part 5 – Benefit-risk assessment

Introduction

Cortaderm is a cutaneous spray solution containing one active substance - hydrocortisone aceponate. Hydrocortisone aceponate is a well-known active substance.

The active substance, hydrocortisone aceponate, is a di-ester of hydrocortisone with acetic acid at the 21-position and propionic acid at the 17-position. It is a corticosteroid hormone. Topical hydrocortisone is used for its anti-inflammatory or immunosuppressive properties to treat inflammation due to corticosteroid-responsive dermatoses. The product is intended for use in dogs

for symptomatic treatment of inflammatory and pruritic dermatoses and for alleviation of clinical signs associated with atopic dermatitis. The route of administration is cutaneous. The proposed daily dose is 1.52µg of hydrocortisone aceponate/cm^2 of affected skin per day; the treatment to be repeated daily for 7 consecutive days.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

The application is in accordance with Article 13(3) of Directive 2001/82/EC, hybrid application.

Benefit assessment

Direct therapeutic benefit

Hydrocortisone aceponate is a dermocorticoid with a potent intrinsic glucocorticoid activity which means a relief of both inflammation and pruritus leading to a quick improvement of skin lesions observed in case of inflammatory and pruritic dermatosis.

Bioequivalence cannot be demonstrated through bioavailability studies and thus Article 13(3) of Directive 2001/82/EC – hybrid application, applies. Cortaderm can be considered a hybrid product and equivalence with the reference product is fully demonstrated. The direct therapeutic benefits for the test product Cortaderm are expected to be the same as those for the reference product Cortavance.

Additional benefits

No additional benefit identified.

Risk assessment

Quality

Overall, information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The spray pump has been sufficiently characterised and shown to deliver a dose similar to that of the reference product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Risks for the target animal:

Given that the formulation and dosing of Cortaderm and the reference product can be considered identical, equivalence with the reference product is accepted. The risks associated with the use of the product in the target species are the same as for the reference product.

Risk for the user

The use of the product does not entail a greater risk for the user than that of the reference product. The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment

Cortaderm is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, and environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication for the target species dog: for symptomatic treatment of inflammatory and pruritic dermatoses.

As per the latest variation of the reference product Cortavance the following indication has been added to the application of Cortaderm: For alleviation of clinical signs associated with atopic dermatitis.

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for Cortaderm is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.