14 February 2024
EMA/84275/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Alcort (EMEA/V/C/006143/0000)

INN: Hydrocortisone aceponate

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

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Introduction

The applicant Nextmune Italy S.r.l. submitted on 5 October 2022 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Alcort, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 June 2022.

At the time of submission, the applicant applied for the following indications:

For symptomatic treatment of inflammatory and pruritic dermatoses in dogs.
For alleviation of clinical signs associated with atopic dermatitis in dogs.

The active substance of Alcort is 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.

The target species are dogs.

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

The rapporteur appointed is Niels Christian Kyvsgaard and the co-rapporteur is Katarina Straus.

The dossier has been submitted in line with the requirements for submissions under Article 19 of Regulation (EU) 2019/6 – a hybrid application.

The reference product is the centrally authorised veterinary medicinal product Cortavance 0.584 mg/ml cutaneous spray solution (EU/2/06/069) which was first granted a marketing authorisation on 9 January 2007.

On 14 February 2024, the CVMP adopted an opinion and CVMP assessment report.

On 8 April 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Alcort.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with reference number PSMF_NXTMUIT_01, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Manufacture of the active substance testing takes place at a site within the EU. A declaration has been provided for the active substance manufacturer and intermediate manufacturer from the Qualified Person (QP) at the EU batch release site stating that the active substance is manufactured in compliance with EU GMP. This was verified based on an audit performed in September 2020 by Floris Veterinaire Produkten BV. The QP declaration also references an audit of the manufacturing site of the active substance intermediate performed March 2022.

GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, has been provided.

Finished product:

Batch release takes place at:
Floris Veterinaire Produkten BV
Kempenlandstraat 33
5262GK Vught
The Netherlands

Also, sites of quality control testing (microbiological) and site of release testing (chemical and physical) are authorised.
GMP certification, which confirms the date of the last inspection and shows that the sites are authorised for the activities indicated above, has been provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in general in line with legal requirements.

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 is used, as described in section 2 of the SPC.

The product is available in a HDPE bottle with 76 ml of product, closed with a white sprayhead with transparent cap and LDPE/PP dip tube or a white plastic screw cap and a pump spray. The pack size is based on the reference product.

Containers and closure system

The container closure system will be an HDPE round bottle, which will be closed with two different type of closures i) PP screw cap with PE foam sealing inlay with a Teflon coating and ii) spray nozzle + LDPE/PP dip tube + cap. The specification of the primary packaging, ID and dimensions, are

included. Certificates of analysis have been provided demonstrating compliance with the proposed specifications.

The primary packaging components comply with the relevant EU Regulations, e.g. Commission Regulation (EU)10/2011 on plastic materials and articles intended to come into contact with food, and compliance with Ph. Eur. has been also claimed. The applicant has submitted migration studies at 25°C / 60%RH (normal conditions) and 40°C / 75%RH (accelerated conditions). The identified leachable and their concentrations did not give reason for concerns for the animal nor user.

Development of the finished product has focused on the choice of container closure system and functionality of the spray pump. Spray volume and spray pattern of the finished product have been shown to be comparable with the reference product.

Product development

The finished product was developed to mimic the reference product, i.e. it contains the same type of solution, same concentration of active substance, and the same excipient, propylene glycol methyl ether, supporting a biowaiver. The excipient is a non-pharmacopoeial substance, but it is not a novel excipient. It is also included in the section 2 of the SPC.

Physicochemical characteristics like particle size and polymorphism are not critical for this finished product, as the active substance is dissolved.

Batch comparison in terms of appearance, density, identification, assay, and related substances has been performed on a number of batches. 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.

Description of the manufacturing method

The manufacturing process consists of two main steps: Dissolution of the active substance in propylene glycol methyl ether (PGME) and filling. The process is considered to be a standard manufacturing process. The description includes information on process parameters, IPC, and equipment. A bulk holding time has been supported by data.

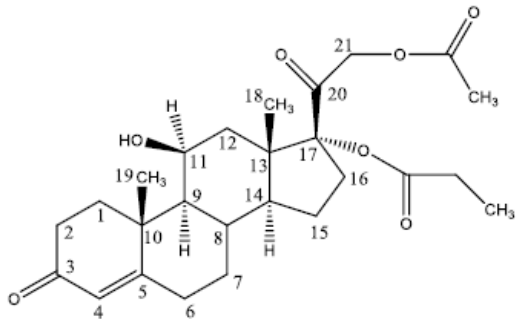
The manufacturer also acts as the batch release site.

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

Validation data have been presented for two small scale batches. The applicant has confirmed they will perform the manufacturing process validation on 3 consecutive large scale production batches prior to marketing of the finished product. The process validation scheme is included in the dossier.

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 ºC to 153 ºC
Specific optical rotation:	+66.5º to +69.0º (10 mg/ml, in dioxane), calculated with reference to the dried 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 exhibits two distinct physical forms β and α modification. The Hovione manufacturing process yields the β modification.

The active substance Hydrocortisone aceponate is not covered by a Ph. Eur. monograph. The documentation of the active substance is presented as an Active Substance Master File (ASMF) with the.

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 completed.

Impurity profile and other relevant sections of the ASMF 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 2 years/ at 5°C±3°C, protected from light is supported by the stability data and is acceptable.

Excipients

The excipient propylene glycol methyl ether is a non-pharmacopoeial substance. The in-house specification is acceptable. The analytical procedure for assay and related substance (2-methoxy 1-propanol) is described and validated. Two certificates of analysis have been provided.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 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 finished product release specification controls relevant parameters for the dosage form, i.e. appearance, colour, clarity, density, water content, identification of active substance, related substances (each individual and total), filling volume, microbiological purity uniformity of delivered mass, and the specification has been assigned a version number and date.

Analytical procedures have been described and validated. Stress studies have been performed showing that the active substance is degraded upon exposure to heat, acid, basic and oxidative conditions. Mass balance is maintained.

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

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the CVMP guidance on risk management requirements for elemental impurities in veterinary medicinal products. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

Stability

Stability data from commercial batches of finished product stored under long term conditions for 9 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH have been provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The specification parameters proposed at the end of shelf-life are the same as those proposed at release, but limits for colour, water content and related substances differ from the release specification. Widening of the specification limits is justified.

The analytical procedures used are stability indicating.

A small increase in total related substances is noted, i.e. up to 0.4 % after 18 months at long term

and up to 0.7 % after 6 months at accelerated storage conditions. For all other parameters no change to their upper or lower limits have been noted. A shelf-life on 36 months is acceptable based on the available stability data. No storage condition is required.

The finished product is sensitive for exposure to photo light, but it is suitably protected by the container closure system.

Stability data to support an in-use period of 6 months have been provided. The in-use period is included in the SPC.

Overall conclusions on quality

The finished product is a cutaneous spray, solution containing 0.584 mg/ml of the active substance hydrocortisone aceponate. It is packaged in HDPE bottle with 76 ml of product, closed with a white spray-head with transparent cap and LDPE/PP dip tube or a white plastic screw cap and a pump spray. The pack size is based on the reference product.

The reference product Cortavance and the candidate product Alcort are both cutaneous solutions containing the same concentration of active substance and excipient and present the same physico-chemical characteristics.

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.

The applicant has confirmed that they will perform manufacturing process validation on 3 consecutive large scale production batches prior to the marketing of the finished product.

Part 3 – Safety documentation (Safety and residues tests)

Alcort is a solution for symptomatic treatment of inflammatory and pruritic dermatosis as well as for the alleviation of clinical signs associated with atopic dermatitis 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". Similar formulations have been used in veterinary medicine for more than 10 years. Since bioequivalence cannot be demonstrated for this topically applied product through bioavailability studies, the application was therefore submitted under Article 19(1) of Regulation (EU) 2019/6, i.e. hybrid application, and the applicant has demonstrated pharmaceutical equivalence. It can therefore be accepted that the safety profile for the candidate product will be the same as that which exists for the reference product.

The product is intended for cutaneous administration and is of the same type of solution, contains the same concentration of the active substance (0.584 mg/ml of hydrocortisone aceponate) and the same excipient (the solvent propylene glycol methyl ether) as Cortavance. The difference in the amount of excipient, if any, is not expected to affect the rate and/or extent of absorption of the active substance. 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 Alcort. The delivered dose and spray pattern are also considered to be similar between reference and test product. In line with the above, 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 Alcort and the reference product. Please also refer to part 4 for further details.

Safety tests

As pharmaceutical equivalence with the reference product is accepted, the pharmacological effects of this product are deemed to be identical to those of the reference product. Alcort and Cortavance can be considered equivalent, and pharmacological and toxicological studies are not required. The toxicological aspects of this product are thus considered identical to those of the reference product.

The product contains the same excipient 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

A user safety exposure assessment and calculation were submitted in accordance with the "Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014). However, since Alcort and its use are considered to be equivalent to the reference product, a user safety risk assessment was not required.

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. The special precautions for the handler stated in the summary product characteristics (SPC) of Alcort are identical to those stated in the SPC of Cortavance.

Environmental risk assessment

The environmental risk assessment (ERA) of the pharmaceutical product was performed according to the relevant guidance documents, 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 that no phase II is required, since 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.

Overall conclusions on the safety documentation: safety tests

As bioequivalence cannot be demonstrated through bioavailability studies, the application was submitted under Article 19(1) of Regulation (EU) 2019/6, i.e. hybrid application. It is considered that results of toxicological or pharmacological tests are not required for Alcort, since pharmaceutical equivalence with the reference product is accepted (see part 4 below).

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.

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 the same 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 candidate and reference product are not expected to have an impact on the safety of the candidate product. Also, the similarity of the delivered dose and the spray pattern between the reference and the test product has been confirmed. 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 for Alcort has been submitted as a hybrid application under Article 19(1) of Regulation (EU) 2019/6. The reference product is the centrally authorised product Cortavance 0.584 mg/ml cutaneous spray solution for dogs. Alcort 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 (dogs) and are to be administered by the same dosing regimen.

Pre-clinical studies

No data provided due to the legal basis of the application.

Pharmaceutical equivalence

Alcort is of the same type of solution, contains the same concentration of the active substance and the same excipient as the reference product Cortavance, and is intended for use in the same indications as Cortavance.

Alcort is a cutaneous spray solution with locally acting effect, and therefore in vivo bioequivalence cannot be determined for this topical formulation using an *in-vivo* bioequivalence study. However, 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 2).

Both products are simple solutions of hydrocortisone aceponate in propylene glycol methyl ether with no other excipients. The difference in the amount of excipient, if any, is not expected to affect the rate and/or extent of absorption of the active substance. The manufacturing process is very simple and any potential differences between the manufacturing process of the candidate and reference product are not expected to impact the efficacy and target animal safety of Alcort.

Both Alcort and Cortavance are supplied with a spray pump to facilitate the cutaneous administration. To be able to assume pharmaceutical equivalence, the candidate product needs to provide the same dosage and spray pattern as the reference product. In part 2 of the assessment, it is concluded that

the two devices had similar spray patterns and hence can be considered to provide the same amounts of product.

Therefore, the candidate and reference product can be considered pharmaceutically equivalent.

Pharmacology

Pharmacodynamics/Pharmacokinetics

No proprietary data was provided since this is an application submitted in accordance with Article 19(1) of Regulation (EU) 2019/6. 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, and the absence of data is accepted.

Target animal tolerance

No data from specific tolerance studies are presented for Alcort. However, 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 Alcort 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 trial(s)

No clinical efficacy studies were provided. 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 conclusions on efficacy

Alcort 0.584 mg/ml cutaneous spray solution for dogs is a hybrid application submitted in accordance with Article 19(1) of Regulation (EU) 2019/6.

The reference product, Cortavance, and the candidate product, Alcort, are both cutaneous solutions containing the same qualitative and quantitative composition of active substance and the same excipient in similar amount and present the same physico-chemical characteristics. The delivery dose and spray pattern were demonstrated to be 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

Alcort 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 1.52 µg of hydrocortisone aceponate/cm^2 of affected skin per day; the treatment to be repeated daily for 7 consecutive days for treatment of inflammatory and pruritic dermatoses and for at least 14 and up to 28 consecutive days for alleviation of clinical signs associated with atopic dermatitis.

The application has been submitted in accordance with Article 19 of Regulation (EU) 2019/6 – hybrid application.

Benefit assessment

Direct 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 the application was submitted under Article 19(1) of Regulation (EU) 2019/6 – hybrid application. Alcort can be considered a hybrid product and pharmaceutical equivalence with the reference product is fully demonstrated. The direct therapeutic benefits for the Alcort 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 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:

In light of the formulation and dosing of Alcort and the reference product, equivalence of the products 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

Alcort 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 in dogs. For alleviation of clinical signs associated with atopic dermatitis in dogs. 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 to date, 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) considers that the application for Alcort is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6).

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.