21 June 2018
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Cortacare (EMEA/V/C/004689/0000)

International non-proprietary name: 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 Animalcare Ltd submitted on 16 May 2017 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Cortacare through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 November 2016 as the product would constitute a hybrid product of a product authorised through the centralised procedure Cortavance.

The applicant applied for the following indication: for symptomatic treatment of inflammatory and pruritic dermatoses in dogs.

The active substance of Cortacare is hydrocortisone aceponate, a corticosteroid which relieves both inflammation and pruritus leading to a quick improvement of skin lesions observed in case of inflammatory and pruritic dermatoses. The target species is dogs.

Cortacare is a cutaneous spray solution that contains 0.584 mg/ml hydrocortisone aceponate and is presented in packs containing 1 bottle with 76 ml of solution.

The rapporteur appointed is Sylvie Louet and the co-rapporteur is Wilhelm Schlumbohm.

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

A request to change the applicant, Animalcare Ltd (United Kingdom), during the assessment procedure was exceptionally accepted as a result of the expected exit of the United Kingdom from the European Union on 30 March 2019. The new applicant is Ecuphar NV (Belgium).

On 21 June 2018, the CVMP adopted an opinion and CVMP assessment report.

On 27 August 2018, the European Commission adopted a Commission Decision granting the marketing authorisation for Cortacare.

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 detailed description of the pharmacovigilance system (dated 21 September 2016) 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

Manufacture, packaging and analytical testing takes place at a site within the EU. GMP certification, confirming the dates of the last inspection and showing that the site is authorised for the manufacture of such veterinary dosage forms, has been provided.

Batch release of the dosage form take place at Bioglan AB in Sweden.

On the EudraGMP website, a manufacturing authorisation issued on 19 January 2018 by the Swedish Medical Products Agency is available. A GMP certificate, which confirms the date of the last inspection (8 December 2016) and which shows that the site is authorised for batch release of such veterinary dosage forms, is also available on the EudraGMP website.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release which has also taken into consideration the GMP certificate available for the active substance site issued by the Portuguese Health Authorities following inspection.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

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

Part 2 - Quality

Composition

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

The other ingredient is propylene glycol methyl ether (solvent) as described in section 6.1 of SPC.

Containers

The product is available in a polyethylene terephthalate 76 ml bottle closed with a polypropylene screw cap with bore seal and supplied with a spray pump as described in section 6.5 of the SPC.

It was demonstrated that the material of the bottle complies with the EU food legislation requirements. The choice of the container closure system was justified by studying the container's leachables. The specifications proposed for the delivery system, the spray pump, are considered justified. Dose accuracy of the spray pump on filled and half-filled bottles was demonstrated but a high variability was observed when the bottle is almost empty (5 ml). However, similar variability was also observed for the reference product and therefore it is accepted.

The bottle is packed in an outer cardboard box. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

Formulation development studies and data on formulation stability were presented and considered

satisfactory. The excipient is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

The proposed primary packaging was also justified considering the one used for the reference product. Data demonstrating that the spray pump allows the treatment of the surface area indicated in the SPC was presented, with a comparison of the delivered dose and diameter of the surface to be treated (spray pattern) with the reference product (Cortavance). The study report and the individual results of the spray dose test were presented for both products, Cortacare and Cortavance to confirm conclusions on the similarity of the delivered dose between the reference and test product.

Method of manufacture

The manufacturing process consists of the bulk production followed by the filling step. The process is considered to be a standard manufacturing process.

The manufacturing process is considered well described. The in-process controls are considered adequate for this manufacturing process and pharmaceutical form.

The process was validated on two pilot scale batches. Considering that the process is a standard one, the absence of validation on industrial batches is accepted.

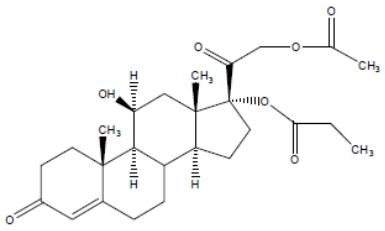
The process validation protocol for industrial batches is presented including the validation of the holding time for the bulk product as part of the manufacturing process validation. The validation protocol is considered acceptable.

Process validation for full scale batches will be generated post-authorisation and will remain available at the manufacturing site for review during routine inspection of the site which is considered acceptable.

Control of starting materials

Active substance

The active substance, hydrocortisone aceponate is a white to slightly yellowish crystalline powder. The active substance is soluble in alcohol and practically insoluble in water and has the following structure:



Hydrocortisone Aceponate

Hydrocortisone aceponate exhibits stereoisomerism due to the presence of 7 chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

Hydrocortisone aceponate shows polymorphism. Only one polymorphic form is obtained with the manufacturing process of the active substance manufacturer. However, the active substance is in solution in the finished product and therefore polymorphism of the active substance is not critical for

this product.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

There is no monograph of hydrocortisone aceponate in the Ph. Eur. so the manufacturer of the active substance elaborated an internal set of specifications.

The characterisation of the active substance and its impurities is considered satisfactory. Potential and actual impurities were well discussed with regards to their origin and characterised. A discussion on potential genotoxic impurities is presented.

Hydrocortisone aceponate is synthesised in one main step from hydrocortisone, followed by one mandatory purification step and two optional purification steps. The starting materials are acceptable with appropriate specifications. Detailed information on the manufacture of the active substance, the controls performed on raw materials, intermediates and during the process has been provided in the restricted part of the ASMF.

Analytical methods used to control the active substance have been validated adequately and described according to VICH GL1 and GL2 by the ASMF holder and the finished product manufacturer.

The active substance specification includes tests for appearance, crystallinity, colour of solution, identity, melting point, specific optical rotation, loss on drying, residue on ignition, heavy metals, assay and impurities.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (15 batches) of the active substance have been provided by the active substance manufacturer. The results are within the specifications and consistent from batch to batch.

During the stability studies, significant changes occurred when hydrocortisone aceponate was stored at 25 °C ± 2 °C/60% ± 5% RH, mainly due to the increase of an impurity. Stability data on 24 batches of active substance from the proposed manufacturer stored in the intended commercial package or in an alternative packaging system for 24 to 60 months under long term conditions at 5 °C ± 3 °C and for up to 6 months under accelerated conditions at 25 °C/60% RH according to the VICH guidelines were provided. Results on stress conditions (acidic, basic, oxidative, thermal and photolytic (UV light and visible light)) were also provided on one batch.

The following parameters were tested: description, related substances and purity. The analytical methods used were the same as for the active substance specification and were stability indicating.

All tested parameters were within the specification. Degradation products increased under accelerated conditions but remained within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months, protected from light and at a temperature between 2 °C and 8 °C in both proposed containers.

Batch testing results from the finished product manufacturer were presented. The results comply with the proposed specification.

Excipients

The only excipient used in the formulation, propylene glycol methyl ether, is a known pharmaceutical ingredient and its quality is compliant with internal specifications. This excipient is included in section 6.1 of the SPC.

The specifications are considered appropriate.

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. The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance (EMA/410/01 rev 3).

Control tests on the finished product

The specifications proposed for the finished product at release are appropriate to control the quality of the finished product. The following parameters are controlled at release: appearance, active substance identity and assay, impurities, microbiology, net fill weight and water content.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards 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 the finished product in accordance with the specifications at release.

Stability

Stability data of two pilot-scale batches of finished product stored under long term conditions for 18 months at 25 °C/60% RH and for up to 6 months under accelerated conditions at 40 °C/75% RH according to the VICH GL3 were provided. The batches used in the stability studies are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the shelf life specifications. The analytical procedures used are stability indicating.

The following parameters are controlled at end of shelf-life: appearance, appearance of packaging, active substance assay, impurities, microbiology and water content.

The limits proposed at the end of shelf-life are the same as those at the time of release except for individual specified and unspecified impurities, active substance assay and water content. The widening of these limits compared to those at release has been appropriately justified.

An in-use stability study is also provided on one pilot batch. Results in compliance with the shelf-life specifications of the finished product were obtained after 6 months after opening.

In addition, one batch was exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products.

Based on all the available stability data, the proposed shelf-life of 2 years as packaged for sale and 6 months after first opening as stated in the SPC is acceptable.

Considering the levels of extractables observed in accelerated conditions and the fact that no toxicological data is submitted on these compounds, the storage precaution "Do not store above 25°C" was added in the product information.

Overall conclusions on quality

In general, 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. Comparison of the delivered dose and spray pattern with the reference product was presented. Data about the dose delivered by two spray pump activations was also provided.

The quality of this product is considered to be acceptable. No TSE risk was identified.

In addition, the applicant is recommended to provide the following information post-authorisation:

- The first 3 batches produced for commercial release should be placed in a stability study.
- The in-use stability study should be performed on a batch close to the end of the proposed shelf-life and the authorities informed in case of out-of-specification results.

As the manufacturing method is a relatively simple standard process and validation data on pilot-scale batches were provided, it was accepted that full scale validation would be performed post-authorisation. In accordance with the Process validation guideline for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1), process validation for full scale batches will be generated post-authorisation and remain available at the manufacturing site for review during routine inspection of the site.

Part 3 – Safety

The product is a solution for a cutaneous spray intended for use in dogs with hydrocortisone aceponate as active ingredient. Hydrocortisone aceponate is a corticosteroid which has been developed as anti-inflammatory and anti-pruritic for dogs with dermatoses. It has been used in veterinary medicine for more than 10 years. The legal basis for this application is Article 13(3) of Directive 2001/82/EC, a hybrid application. A safety file has been provided accordingly.

Cortacare contains the same amount of active substance and excipient as the reference product, and the target species, the therapeutic scheme and the indication 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 Cortacare. The delivered dose and spray pattern are also considered similar between reference and test product. Consequently, no toxicological tests or efficacy studies have been submitted.

To ensure comprehensive adverse event surveillance and to benefit from the possibility of aligning periodic safety update report (PSUR) submissions with the reference product as foreseen in the legislation, PSUR submissions should be synchronised for Cortacare and Cortavance which is currently on a three-yearly reporting cycle. The next data lock point (DLP) for Cortacare is 31 July 2020, followed by 3-yearly PSUR submissions. In addition, surveillance of the data in EudraVigilance Veterinary (EVVet) will also be synchronised for signal detection of the two products.

Safety documentation

As this is a hybrid application according to Article 13(3) and equivalence with the reference product is accepted, results of toxicological tests are not required.

The toxicological aspects of this product are considered identical to the reference product.

Excipients

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

User safety

No user risk assessment has been submitted.

This is acceptable taking into account that:

- this application is submitted in accordance with Article 13(3) of Council Directive 2001/82/EC;
- the product contains the same amount of active substance and excipient as the reference product;
- the target species, the therapeutic scheme and the indication are identical to those of the reference product;
- equivalence with the reference product is claimed (see Part 4).

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, therefore, the same risk mitigation measures as those of the reference product are applied.

Environmental risk assessment

The Environmental Risk Assessment (ERA) of the pharmaceutical product was performed according to the relevant guidelines (VICH GL6 and the CVMP Guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH 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 SPC.

Residues documentation

Not applicable.

Overall conclusions on the safety documentation

As this is a hybrid application submitted according to Article 13(3) of Directive 2001/82/EC, and as equivalence with the reference product is accepted, results of toxicological or pharmacology tests were not required.

The excipient used in the formulation is well known and widely used in pharmaceutical products intended for human and veterinary use and is not considered to be of concern.

An ERA was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

The product contains the same amount of active substance and excipient as 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 Cortacare. The target species, the therapeutic scheme and indication are identical to those of the reference product. The delivered dose and spray pattern are also considered similar between reference and test product. Equivalence is confirmed. 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, therefore, the same risk mitigation measures as those of the reference product are applied.

Part 4 – Efficacy

This is a hybrid application submitted under Article 13(3) of Directive 2001/82/EC. The reference product is the centrally authorised product Cortavance 0.584 mg/ml cutaneous spray solution for dogs.

The reference product, Cortavance, is indicated for symptomatic treatment of inflammatory and pruritic dermatoses in dogs. The recommended dose is 1.52 µg of hydrocortisone aceponate/cm^2 of affected skin per day. This dosage can be achieved with two pump spray activations over a surface to be treated equivalent to a square of 10 cm x 10 cm. The treatment is to be repeated daily for 7 consecutive days.

Pharmacodynamics / Pharmacokinetics

As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC, and as equivalence with the reference product is confirmed, results of pharmacological tests are not required.

The pharmacological properties of this product are considered to be identical to those of the reference product.

Bioequivalence studies

The product is a cutaneous spray solution with locally acting effect. Therefore, an *in vivo* bioequivalence study with the reference product is not applicable.

The two formulations, Cortacare and Cortavance (reference product), are identical in terms of active substance and excipient, and present the same physico-chemical characteristics (pH, relative density). 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 or efficacy of Cortacare. The equivalence of the products is accepted as the pharmaceutical properties (delivered dose and spray pattern) are shown to be equivalent between Cortacare and Cortavance.

Tolerance in the target species of animal

No data from specific tolerance studies are presented for Cortacare.

Since the product contains the same amount of active substance and excipient as the reference product and equivalence with the reference product has been shown, a similar tolerance profile for

both products can be assumed. Consequently, no specific tolerance studies are required for Cortacare. Administration of Cortacare 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.

The text proposed for inclusion in sections 4.6 and 4.10 of the proposed SPC is in line with the text in the authorised SPC of the reference product and is considered acceptable.

Clinical field trials

No clinical efficacy studies were provided. Given the nature of the application (hybrid application according to Article 13(3) of Directive 2001/82/EC) and considering that equivalence is established with the authorised reference product, this is considered acceptable.

Overall conclusion on efficacy

Cortacare 0.584 mg/ml cutaneous spray solution for dogs is a hybrid application submitted according to Article 13(3) of Directive 2001/82/EC.

Cortacare and its reference product Cortavance are both cutaneous solutions containing the same concentration of active substance and excipient and present the same physico-chemical characteristics (pH, relative density). 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 of Cortacare. As equivalence is shown, both Cortacare and the reference product are expected to have similar safety and efficacy profiles in the same indications and posology.

Part 5 – Benefit-risk assessment

Introduction

Cortacare is a cutaneous spray solution containing hydrocortisone aceponate.

The active substance, hydrocortisone aceponate, is a corticosteroid which relieves both inflammation and pruritus leading to a quick improvement of skin lesions observed in case of inflammatory and pruritic dermatoses. The product is intended for use in dogs for symptomatic treatment of inflammatory and pruritic dermatoses. The proposed effective dose is 1.52 µg of hydrocortisone aceponate/cm^2 of affected skin per day.

The application has been submitted in accordance with Article 13(3) of Directive 2001/82/EC (hybrid application). The reference medicinal product is Cortavance (EU/2/06/069/001-002) which was authorised by the European Commission in January 2007.

Benefit assessment

Direct therapeutic benefit

Cortacare contains hydrocortisone aceponate as active substance.

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

Since Cortacare is a hybrid application and equivalence with the reference product is fully demonstrated, the direct therapeutic benefits for Cortacare are expected to be the same as those for the reference product Cortavance, i.e. efficacy in the symptomatic treatment of inflammatory and pruritic dermatoses in dogs.

Additional benefits

No additional benefit identified.

Risk assessment

Quality:

In general, information on development, manufacture, control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

Safety:

Risks for the target animal:

Given the similarity of the formulations of Cortacare and the reference product and that equivalence with the reference product is fully established, the risks associated with the use of the product in the target species are the same as for the reference product. Administration of Cortacare 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.

Risk for the user:

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

Risk for the environment:

Cortacare 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.

To ensure comprehensive adverse event surveillance, signal detection and PSUR submissions will be synchronised with those for the reference product, Cortavance.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for symptomatic treatment of inflammatory and pruritic dermatoses in dogs.

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 product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Cortacare 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.