EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Cortavance (EMEA/V/C/000110/II/0015)

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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Product profile

Invented name:	Cortavance
Active Substances:	hydrocortisone aceponate
Target Species:	Dogs
Pharmaceutical Form:	Cutaneous spray, solution
Strength:	0.584 mg/ml
Therapeutic Indication:	For symptomatic treatment of inflammatory and pruritic dermatoses in dogs. For alleviation of clinical signs associated with atopic dermatitis in dogs.
ATCvet code	QD07AC16
Pharmacotherapeutic group	Corticosteroids, dermatological preparations
Applicant	Virbac S.A.

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Virbac S.A. (the Applicant), submitted to the European Medicines Agency (the Agency) on 30 April 2020 an application for a type II variation for Cortavance.

1.2. Scope of the variation

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To add a new therapeutic indication: "for symptomatic treatment of atopic dermatitis in dogs".

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

Canine atopic dermatitis (cAD) is a common, highly pruritic disease characterised by a waxing and waning course with frequent flares of inflammation. Treatment of severe and chronic cAD cases can be challenging, and in general requires multimodal medical, nutritional and other supportive interventions.

Cortavance (hydrocortisone aceponate) spray was first authorised in 2007 for symptomatic treatment of inflammatory and pruritic dermatoses in dogs. The recommended dosage is 1.52 µg of hydrocortisone aceponate/cm^2 of affected skin daily for 7 consecutive days. The present variation application is to add a new therapeutic indication for symptomatic treatment of atopic dermatitis, and the applicant suggests a prolonged treatment with the same dose for up to 28 consecutive days.

2.1. Safety

User safety

No new studies were presented but existing data were reanalysed and new literature references were submitted and analysed in accordance with the CVMP Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014) for the present application.

The acute toxicity of Cortavance is very low with an oral LD_{50} = 2150 mg/kg in mice and a dermal LD_{50} > 4000 mg/kg in mice and rats.

A Toxicological Reference Value (TRV) was selected based on the endogenous basal hydrocortisone production levels in humans derived from literature studies. Several literature references were reviewed with respect to basal endogenous hydrocortisone levels in different populations and age groups and the lowest encountered was chosen as the reference value. The lowest level of hydrocortisone measured was 82 µg/kg bw/day (range 82 – 483 µg/kg bw/day), which corresponds to 104 µg/kg bw/day hydrocortisone aceponate. For comparison, the therapeutic dose for humans suffering from adrenal insufficiency is 20-30 mg/day hydrocortisone oral dosing.

An accidental exposure of the user to the product represents an addition of hydrocortisone to the physiological basal level, and an estimate of an additional amount of exogeneous hydrocortisone not eliciting a pharmacological effect is based on a study measuring human fluctuations of cortisol level in hair. In addition to circadian and seasonal changes, individuals showed unseasonal fluctuations averaging about 22% around their baseline hair cortisol. Hence, an additional 10% of hydrocortisone above the lowest measured human basal level is regarded as safe. No intraspecies variability factor is applied as the lowest basal human hydrocortisone level is regarded as representing worst case scenario. The safe level of user exposure to hydrocortisone resulting from use of the product is therefore considered to be 8.2 µg/kg bw/day (or 10.4 µg hydrocortisone aceponate per kg bw/day).

Since the TRV is based on human basal systemic exposure of hydrocortisone, the chronic toxicity has been accounted for by this approach. Studies have proven that the product has no skin irritation and skin sensitisation at dermal exposure but it is classified as an eye irritant.

The human oral and dermal bioavailability of the product are unknown and 100% systemic bioavailability is assumed, which especially for the dermal absorption is considered very conservative. For reference, the dermal bioavailability in dogs is 0.2% and in rats, guinea pigs and rabbits 20-40%. The dermal and oral exposure is calculated in accordance with the CVMP Guideline on user safety of topically administered veterinary medicinal products. Hence, in the application phase an adult could be exposed to 0.025 µg HCA/kg bw by hand to mouth transfer and 0.25 µg HCA/kg bw dermally and in the post-application phase a short-term oral plus dermal exposure of a child could be 1.65 µg HCA/kg bw. All exposure scenarios are regarded as being safe (i.e MOE greater than 1 compared to the TRV).

Concerning the user safety of pregnant woman, which is considered to represent the worst case scenario for adults, literature studies on teratogenic effects in humans were reviewed and some suggested an association between systemic corticosteroids treatment during pregnancy and cleft palate in the foetus. Other studies were not able to confirm this association. It is noted that the corticosteroids investigated in the human studies are mainly synthetic which are more potent than hydrocortisone, different routes of administration are included and the doses administered are therapeutic doses. A quantitative risk assessment on teratogenicity was performed based on the fact that enzymes in the cells of the placenta convert 80-90% of the maternal cortisol to the inactive cortisone before translocating to the foetal blood system; this is in line with another reference showing that 15% of cortisol crosses the placenta unmetabolized. The maternal/foetal ratio for plasma cortisol is on average 11.4 and the plasma cortisol levels in pregnant women increase threefold in the third trimester.

The endogenous basal level of cortisol in the human foetus is therefore estimated to be 82/11.4 = 7.19 µg/(kg bw × day). Considering that 15% of a 10% additional exposure above the basal level in the woman (82 x 0.10 = 8.2 µg/kg bw) would be transferred to the foetus, the amount added the basal level of the foetus is estimated at 82 x 0.10 x 0.15 = 1.23 µg/kg bw. This translates into 1.23/7.19 = 17.1% cortisol added to the basal level in the foetus which is unacceptable. A relative Teratogenic Safety (TS%) value (or threshold for teratogenicity) ensuring that cortisol will not increase by more than 10% in the foetus is calculated as follows:

$$TS\% = \frac{\frac{82}{11.4} \times 0.1}{82 \times 0.15} = \frac{0.1}{11.4 \times 0.15} = 5.85\%$$

which corresponds to 82 x 5.85% = 4.8 µg hydrocortisone/kg bw or 104 x 5.85 = 6.1 µg HCA/kg bw added to the basal level in a pregnant woman.

The TRV for estimating the risk of pregnant women exposed to the Cortavance formulation should therefore be set at 6.1 µg HCA/kg bw day.

Hence, the margin of exposure calculated for worst case indirect oral exposure (0.025 µg/kg) is 244 and for worst case direct dermal exposure (0.25 µg/kg) is 24, which is acceptable considering that the margin must be greater than one. The risk assessment concludes that accidental exposure of pregnant woman to Cortavance does not pose a teratogenic risk.

In relation to the possibility of accidental exposure of a child, the worst case scenario was considered to be application of one actuation directly into the mouth. Assuming a 12.5 kg child, this results in an exposure of 6.1 µg/kg bw and a MOE of 1.7 (using the TRV of 10.4 µg HCA per kg bw), which is above one and so is acceptable. It is noted that a MOE greater than 1 would not be achieved if the child were to remove the pump and ingest the product directly from the bottle. However, this is considered to be a very unlikely scenario and is adequately mitigated by statements in the product information.

Ocular exposure is possible during the application phase and a safety warning is included in the SPC. The risk of inhaling the active substance via evaporation is non-existent as hydrocortisone aceponate is non-volatile at ambient temperature. There is a risk of inhaling the vehicle 1-methoxypropanol-2 but the estimated exposure of the user is approximately 288 times lower than the occupational exposure limits. The occupational exposure limits were set according to Commission Directive 2000/39/EC of 8 June 2000 at 150 ppm, at which 2.5 hours of exposure elicited eye irritation and no systemic effects. The worst-case exposure by inhalation of evaporated 1-methoxypropanol-2 is estimated to be 0.52 ppm. The risk of inhaling the product via droplets during application has been assessed in the original application and applicant was asked to calculate the risk of exposure applying the current guidelines. The droplet size distribution has been measured and the respirable fraction is 10% of a pump spray. A quantitative risk assessment based on a worst-case scenario featuring a pregnant woman in a small room (10 m^3) with no ventilation and with and inhalation rate during light exercise of 0.477 m^3 over 20 min exposure, treating one third of a medium sized dog and assuming 100% human bioavailability results in an exposure to hydrocortisone aceponate of 0.26 µg/kg bw and an exposure to the vehicle of 0.032 ppm (0.232 µL/kg bw). There is therefore not considered to be an undue risk of accidental inhalation. As a further precaution, the SPC states "*To avoid inhalation of the product, apply the spray in a well-ventilated area".*

Application and post-application exposure scenarios were evaluated for both adult and child, and the possible identified risks are addressed appropriately in the SPC.

2.2. Efficacy

2.2.1. Target animal safety

The evaluation of safety in dogs is based on data derived from different sources.

The pivotal target animal safety study was conducted in 2004 and evaluated the local and general tolerance of Cortavance following a daily dermal application to beagle dogs for 2 weeks. Twenty-four healthy dogs, aged 7-9 months were dosed with placebo, 1X, 3X or 5X the recommended dose (flanks, estimated ~1500 cm^2, corresponding to approx. 1/3 of the total of the dog body surface).

Lymphocyte counts were significantly decreased in the 3X and 5X dose groups compared to controls. A significant decrease in blood adrenocorticotropic hormone (ACTH) and cortisol concentrations was observed in animals in 3X and 5X groups on Days 8 and 15. A significant dose-related decrease in adrenal gland weights was found. Skin thickness was studied and it was concluded that no difference in the thickness of the epidermis and epidermis + dermis was observed between control and treated groups. It is noted that the duration of this study (14 days) was shorter than the proposed duration of treatment of atopic dermatitis (28 days).

In a recovery study with 12 dogs, the post-ACTH cortisol concentrations of the 3X and 5X groups were similar to the control group 7 and 9 weeks, respectively, after cessation of treatment (original dossier).

Safety was also evaluated in clinical studies. In one clinical study (Nuttall et al., 2009; Ref. 1), safety measures included haematology, biochemistry and ACTH stimulation test. None of the tested dogs (n=9 from the treatment group) showed changes to blood parameters at D28 and D70, and, in particular, all had pre- and post-ACTH cortisol levels within normal ranges. The study was not a designated safety study, the applied dose was limited, and so was the number of dogs treated daily with the label dose for more than 28 days (2 dogs were treated for 70 days). No skin biopsies were taken, but no macroscopic changes were observed at D14 or D28.

In a similar, positive-controlled study (Nutall et al., 2012; Ref. 2), the tolerance of Cortavance spray was evaluated in dogs with canine atopic dermatitis in a single-blind randomized controlled trial; ciclosporin was used as positive control. Twenty-four dogs received Cortavance once daily at the recommended dose for 28 days. Overall, 9 dogs of the Cortavance group were maintained on every-other-day treatment from D28 to D56 whereas 15 dogs were maintained on daily administration. From D56 to D84, 13 dogs of the Cortavance group were maintained on every-other-day or twice-weekly treatment and 11 dogs were treated daily. In total, 10 dogs were treated daily throughout the 84-day period. No adverse events were noted in clinical examinations of dogs treated with Cortavance. However, no skin biopsies or blood samples were taken to study long-term changes to the skin, such as atrophy or suppression of the HPA axis, which may initially be asymptomatic.

Another pilot study investigated the effect of Cortavance spray on skin thickness in 4 healthy beagle dogs after 14 – 56 days of daily treatment. The animals were examined daily for general clinical signs and reaction at application sites. Skin biopsies were taken from treated areas before treatment and then every 2 weeks. A histopathologist blinded to date of sampling evaluated skin histology and performed 5 skin thickness micrometre measurements on tissue sections. The results seem to indicate a trend of reduced skin thickness that was not statistically significant in three out of four dogs, and this was in particular evident at D14 and D28.

Also, slight acanthosis was noted in two dogs on D43. No flattening of epidermal cells, reduction in the number of epidermal cell layers, or follicular atrophy was observed.

An additional relevant study was identified by the CVMP (Bizikova et al.: Effect of a novel topical diester glucocorticoid spray on immediate- and late-phase cutaneous allergic reactions in Maltese–beagle atopic dogs: a placebo-controlled study. Veterinary Dermatology, 2010, 21, 71–80). Ten atopic dogs were sprayed once daily for 14 days in both axillary and inguinal regions, which are areas commonly affected by skin lesions in dogs with cAD. Dogs were randomly assigned to treatment with either hydrocortisone aceponate spray according to label or placebo spray used in the same way. All histological slides were randomized, coded and examined in a blinded fashion.

The study showed a visible skin atrophy in the axillary and inguinal regions of most dogs in the hydrocortisone aceponate group within 14 days of treatment, which was associated with a significantly reduced dermal thickness measured histologically at treated thoracic sides. The reduction in dermal thickness was associated with atrophy of dermal collagen and partial atrophy of adnexa.

Treated sides had decreased numbers of primary and secondary hair follicles in the anagen phase of the hair cycle.

Overall, the combined safety documentation provided by the applicant for use of Cortavance in dogs for a proposed prolonged treatment period from two to four times the current recommended period of time (7 days), that is at least 14 and up to 28 consecutive days, shows an acceptable safety profile (up to 28 days in published clinical studies, although these included relatively few atopic dogs, and histological evaluation of skin changes was not performed). Overdose studies (3X and 5X) in healthy beagles however showed reversible inhibition of the HPA axis for up to nine weeks, while daily label use for 28 consecutive days in one clinical study did not significantly affect responses to ACTH stimulation. In one study, atopic dogs treated daily with label doses for 14 days showed significant, visible skin atrophy, as well as statistically significant reduced skin thickness. A recommendation for an intermediary control by the veterinarian at day 14 to decide if further treatment is needed was therefore included in SPC section 4.9.

However, the safety of treatment for a prolonged period of time beyond the proposed 28 days is not considered to have been substantiated based on the presented evidence. Atopic dermatitis being a chronic condition, an individual risk-benefit evaluation for each dog may be necessary, and frequent re-evaluation of the response and possible side effects must be regularly performed by the attending veterinarian. Appropriate warnings and precautions have been included in the relevant sections of the SPC.

2.2.2. Efficacy for the proposed indication

Two Virbac-funded published studies were submitted as pivotal efficacy studies.

Ref. 1 Nuttall et al. - Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomised, double blind, placebo-controlled trial. Veterinary Dermatology, 2009, 20, 191-198.

This multicentre field study evaluated the efficacy of a 0.0584% hydrocortisone aceponate spray (HCA, Cortavance; Virbac SA) against placebo in canine atopic dermatitis (AD). The treatment was applied once daily at a dose according to SPC for 28 days, with two dogs being treated for a total of 70 days. Dogs with a Canine Atopic Dermatitis Extent and Severity Index, version 3 (CADESI-03)≥ 50 were randomly allocated to receive Cortavance (n = 15) or placebo (n =13) (two sprays from 10 cm away to treat an area of 100 cm^2). CADESI, pruritus (14 cm visual-analogue scale) and owner satisfaction (5-point scale) were recorded every 14 days. Haematology, biochemistry and ACTH stimulation were performed at baseline, day +28 and day +70 (HCA n = 9; placebo n = 7).

Hydrocortisone aceponate spray significantly decreased CADESI score (–61.4% versus –13.4%, p = 0.0069) and pruritus (–38.8% versus +57.6%, p = 0.0015) at D28 compared to placebo. Clinically relevant reductions (>= 50%) were observed in CADESI scores of the Cortavance group in 8 of 15 dogs (53.3%) at Day 14 and 11 of 15 dogs (73.3%) at Day 28. Coat length did not influence the results.

In this study, efficacy of Cortavance was compared to placebo. One dog in the Cortavance group and four dogs in the placebo group were withdrawn during the study, and a last-observation-carried-forward (LOCF) approach was employed in order to carry out the analysis on the Intention to Treat (ITT) population. The approach was explained by the applicant and considered justified. Although the comparison with placebo may be considered of less clinical relevance, the comparison made it possible to separate treatment effect on the clinical outcome from placebo effect.

Twenty-one of the dogs from both groups were enrolled in a dose reduction follow-up (phase 2) after 28 days of treatment until day 70 with different intervals between treatments. When considering only the dogs having received Cortavance daily during the first 28-day period (n=14), only two dogs received Cortavance daily during the second period, 4 dogs received Cortavance every-other-day and the six other dogs were treated twice weekly with Cortavance. Due to the low number of dogs, it is difficult to evaluate the clinical efficacy of treatments in phase 2. Thus, the data from this study do not allow firm conclusions about the efficacy of prolonged treatment past 28 days in atopic dogs.

Ref. 2 Nutall et al. - Comparable efficacy of a topical 0.0584% hydrocortisone aceponate spray and oral ciclosporin in treating canine atopic dermatitis. Veterinary Dermatology, 2012, 23, 4–12.

This GCP-compliant study compared the efficacy of a 0.0584% hydrocortisone aceponate spray (Cortavance; Virbac SA) and ciclosporin in canine atopic dermatitis in a single-blind randomized controlled trial. Twenty-five dogs from 15 breeds and crosses were enrolled in the hydrocortisone aceponate group, and 23 dogs from 10 breeds and crosses in the ciclosporin group. Dogs received Cortavance once daily (two sprays / 100 cm^2; n = 24) or ciclosporin (5 mg/kg; n = 21). The study period was 84 days, with alternative treatment schedules from day 28. Twenty-four dogs received Cortavance once daily at the recommended dose for 28 days and in total 10 dogs were treated daily throughout the 84-day period.

CADESI-03 and pruritus significantly decreased over time (p<0.0001), and there was no difference between the treatment groups (p=0.91 and p=0.52, respectively). By 84 days, every-other-day or twice-weekly therapy was achieved in 13 of 24 hydrocortisone aceponate- and 12 of 21 ciclosporin-treated dogs (p=0.85).

A last-observation-carried-forward (LOCF) approach was also used in this study. However, especially in the context of a non-inferiority design, a per protocol analysis is considered as important as the intention to treat analysis, since the intention to treat analysis might bias results by masking differences. Hence, in order to gain insight into the robustness of results with regard to the LOCF approach, a follow-up analysis based on the per protocol population was carried out. The new analysis confirmed the similarity between Cortavance and ciclosporin groups.

The applicant has used non-parametric tests (Wilcoxon-Mann-Whitney and Wei-Lachan) to compare clinical endpoints for Cortavance treatment with ciclosporin. However, the appropriateness of a non-parametric test for demonstrating non-inferiority in the present context is questionable as it does not assess the size of a difference between groups due to the fact that one does only consider which of two scores is higher but not by how much. This makes it difficult to assess whether a difference is clinically irrelevant or not. The applicant was asked to provide further explanation that the study had sufficient statistical power to actually detect a relevant difference with the employed statistical methods. The applicant performed power calculations and repeated the statistical analysis with a parametric test (t-test). It was noted that the distribution of the score data did not meet the assumption of normal

distribution for the parametric test. The results with the parametric tests are therefore indicative only, but show that a considerably higher sample size would be needed for a formal non-inferiority design. The conclusions based on the t-test follow those using the non-parametric test, i.e. it can be concluded that the study (Ref. 2) showed clinical similarity in the outcome of treatment between Cortavance and ciclosporin groups, although the study did not qualify as a non-inferiority study.

Supportive information: It is noted that only two published clinical studies were provided. In response to the questions raised by the CVMP, the applicant has provided the requested study protocols, raw data and statistical reports concerning the two studies.

In support of the proposed use of the product in section 4.9 of the SPC for proactive therapy, defined as "*treatment of previously affected areas on two consecutive days each week, whether or not lesions are visible at these sites"*, several human references have been provided. The applicant has furthermore presented supportive efficacy information in the form of a treatment recommendation paper from the International Committee on Allergic Diseases of Animals (Ref. 5) and conference proceedings related to topical treatment of cAD (Ref. 6).

One additional published study including atopic dogs was provided by the applicant to support this strategy. The pilot study by Lourenço et al (Efficacy of proactive long-term maintenance therapy of canine atopic dermatitis with a 0.0584% hydrocortisone aceponate spray: a double-blind placebo-controlled pilot study. Vet Dermatol. 2016; 27) was conducted as a randomised, placebo-controlled, double-blinded GCP clinical trial with an end-point of treatment failure. Dogs were treated with Cortavance once daily to remission, then randomly assigned to receive either the HCA spray (n = 21) or a placebo (n = 20) spray on two consecutive days each week. Intention-to-treat analysis was used.

At Day 0, all the dogs were in remission or had mild AD based on their CADESI-03 scores. The time to relapse was significantly higher in the HCA group (median 115 days; range 31–260 days) as compared to the placebo group (median 33 days; range 15–61 days) ($p < 0.0001$). Fifty days after the beginning of Phase 2, more than 85% of the placebo group had relapsed in comparison to only two dogs (11%) of the HCA group. Relapse rates in the HCA group were 60% at 100 days and 80% at 180 days.

Skin biopsies or ACTH-stimulation tests were not performed, but there was no clinical evidence of cutaneous atrophy or secondary infection, although cutaneous atrophy following 14 days of daily treatment has been reported in atopic dogs, and reversible HPA-suppression was seen in 14 days overdose studies (Bizikova et al. 2010, TAS study).

Whilst the concept of proactive intermittent therapy is well-established in human medicine, the same cannot be directly applied for canine AD at present. Based on the evidence presented, the use of this approach or other intermittent treatment regimen in dogs for more than 28 days should be decided case by case by the attending veterinarian. Therefore, a general recommendation in this regard has not been included in the product literature, since this would warrant for additional and longer-term studies of safety and efficacy.

In conclusion, the provided combined evidence presented by the applicant suggests that treatment of dogs with atopic dermatitis for at least 14 days and up to 28 days with the recommended dose provides significant improvement of skin lesions and pruritus in these patients. Appropriate advice and instructions have been included in the product literature. Following the assessment of the data presented by the applicant, the proposed indication "for symptomatic treatment of atopic dermatitis in dogs" was considered too broad and consequently it was amended to "for alleviation of clinical signs associated with atopic dermatitis in dogs".

In addition, the applicant takes the opportunity to update the list of local representatives.

3. Benefit-risk assessment of the proposed change

Cortavance is authorised for symptomatic treatment of inflammatory and pruritic dermatoses in dogs. The active substance is hydrocortisone aceponate, a dermocorticoid with a potent intrinsic glucocorticoid activity. The product is a cutaneous spray solution presented in bottles filled with 31 ml or 76 ml of solution.

The proposed variation is to add a new therapeutic indication: "for symptomatic treatment of atopic dermatitis in dogs". However, following the assessment of the data presented, the proposed indication was considered too broad and therefore it was reworded to "for alleviation of clinical signs associated with atopic dermatitis in dogs".

3.1. Benefit assessment

Direct therapeutic benefit

The pivotal bibliographic studies support the chosen dose and the duration of treatment. Significant improvement of the skin condition and reduction of itching was demonstrated in two peer-reviewed publications, in a representative (but relatively small) group of atopic dogs under controlled conditions, and results indicated comparable efficacy between Cortavance and an authorised comparator product. In another publication, a clear trend for superiority of topical hydrocortisone aceponate treatment over placebo was demonstrated for 28 days.

In conclusion, the product is considered sufficiently effective for the alleviation of clinical signs associated with atopic dermatitis in dogs.

Additional benefits

The additional benefit of treating locally with a corticosteroid is the reduction in the need of treating systemically and the possibility of combining treatments utilising Cortavance as an add on.

The topical treatment offers a possible alternative for owners having difficulties dosing their dog via the oral route and thereby increases the range of available treatment possibilities for pruritic dogs.

3.2. Risk assessment

Safety:

Risks for the target animal:

Based on the reviewed references and previous TAS studies, local adverse effects such as skin atrophy cannot be entirely ruled out in individual dogs. A clinical follow-up visit after 14 days of treatment is therefore recommended in section 4.9. of the SPC. The bioavailability of the topically applied dose after 7 days of daily treatment is 0.2%. Depression of the hypothalamic-adreno-pituitary axis, decreased weight of the adrenal gland and decreased numbers of lymphocytes were registered in high dosed studies. Concerns are that long-term glucocorticoid side-effects might be a risk. Since no dedicated target animal safety study covering the 28 days as applied for plus a margin of extended treatment duration has been submitted, treatment beyond this period must be according to the benefit-risk assessment of the attending veterinarian.

For the currently marketed indication and recommended dosing regimen, administration of hydrocortisone aceponate is generally well tolerated.

Risk for the user:

Cortavance is in general of low toxicity to humans. The risk that hydrocortisone will elicit a systemic pharmacological effect at high exposure rates has been adequately addressed. The formulation is an eye irritant. Appropriate risk mitigation text and warnings have been included in the product information.

Risk for the environment:

Cortavance is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is already included in the SPC and other product information.

In general, it is acknowledged that pharmacovigilance data from previous use in dogs for the original indication suggest that Cortavance spray is well tolerated systemically and locally at the proposed dose for short-term treatment. On the basis of submitted data in support of the current application and assessed safety risks, it is concluded that the proposed prolonged treatment (up to 28 days) is regarded as being safe for the target animal, the user and the environment.

3.3. Risk management or mitigation measures

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

User safety:

User safety risks have been identified as those associated with ocular exposure and those associated with children becoming accidentally exposed to large quantities of the drug product. These risks are mitigated by the safety warnings in the SPC and other product information.

Environmental safety:

No risks have been identified.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality and environmental safety.

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

The product has been shown to be efficacious for alleviation of clinical signs associated with atopic dermatitis in dogs.

The product 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.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Cortavance can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication: "for alleviation of clinical signs associated with atopic dermatitis in dogs". The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of this variation, sections 4.2, 4.3, 4.4, 4.5, 4.9, 4.10 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly. In addition, the applicant takes the opportunity to update the list of local representatives.