SCIENTIFIC DISCUSSION

QUALITY

Composition of the Veterinary Medicinal Product

The proposed product has been developed as a cutaneous spray solution containing 0.5842 mg of hydrocortisone aceponate per ml. The recommended dosage 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 composition is adequately described though the content of active substance is expressed in terms of the salt, hydrocortisone aceponate, rather than hydrocortisone base. This is not in accordance with the normal rules for expression of an active substance present in salt form but had been agreed at the time of submission in accordance with agreements for hydrocortisone preparations in general.

Drug Substance

Hydrocortisone aceponate is manufactured by Hovione FarmaCiencia SA, Loures, Portugal. The synthesis has been described in sufficient detail. Detailed information regarding the manufacture of starting material, including impurity profiles and the possible carry-over of impurities to final active substance, have been addressed. Starting material solvents and reagents have been described with appropriate specifications. Intermediates are adequately controlled.

The drug substance has been sufficiently characterised. A reasonable specification is provided. Impurities including residual solvents and catalyst are adequately controlled and limited in line with VICH requirements.

All analytical methods are adequately described and sufficient validated in line with VICH requirements.

Hydrocortisone aceponate is a relatively stable substance showing no significant sign of degradation after 12 months storage under VICH long term and accelerated conditions. As modest instability was noted on exposure to light, it is recommended that the drug substance be stored protected from light. Stability data, provided for the active substance, supports the proposed re-test period of 12 months when stored in the original package.

Drug Product

The composition of the above product is adequately described.

The product will be manufactured and released by Virbac S.A. in France.
The container/closure system is suitable. Satisfactory data, provided for pump, demonstrate that the pumps can accurately and precisely deliver the required dose volumes at the in-use period of 6 months.

The development pharmaceutics are overall considered sufficient.

Satisfactory documentation is provided for the excipient.

No starting materials which enter the composition of the finished product, nor materials which are used during the manufacturing process fall within the scope of the guidance “Note for guidance on minimising the risk of Transmitting animal Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products” (EMEA/410/01).

The manufacturing process is considered a standard process for obtaining a simple solution of the active substance in a single excipient. A maximum holding time of 5 days in a closed stainless steel tank for the bulk drug product is specified.

The validation data on pilot scale batches are sufficient to ensure a robust manufacturing process. A validation protocol scheme for the first three production batches is provided.

The release and shelf-life specifications comply in general with VICH guidelines and the Ph.Eur. general method for “Veterinary Liquid Preparations for Cutaneous Application. Related substances are satisfactorily controlled. Omission of a test for preservative efficacy has been satisfactorily justified.

Methods for controlling the finished product are adequately described and sufficient validated in line with VICH requirements.

Finished product has been shown to be reasonably stable under test conditions and a proposed shelf-life of 2 years can be established with no special storage conditions.

SAFETY

Pharmacological Studies

Pharmacokinetics

The pharmacokinetic studies conducted in laboratory animals are evaluated in this section. For an evaluation of the pharmacokinetic studies conducted in dogs see this section under the efficacy assessment.

Following a single dose administration the total radioactivity in blood was higher after subcutaneous than after topical administration for hydrocortisone aceponate and hydrocortisone in rats and rabbits. Following topical administration higher levels of radioactivity were found for hydrocortisone aceponate compared to hydrocortisone, while the reverse was true following subcutaneous administration. For both routes of administration the highest concentrations of hydrocortisone aceponate or hydrocortisone were generally found in the gastro-intestinal tract followed by the liver and kidneys. The highest levels of radioactivity were found following subcutaneous administration. In rats, no differences in the relative degree of tissue distribution were noted between hydrocortisone aceponate and hydrocortisone. In rabbits, the radioactivity in tissues was generally higher following hydrocortisone at 6 hours and higher following hydrocortisone aceponate at 30 hours post subcutaneous administration, while the tissue radioactivity was highest following hydrocortisone aceponate at both time points post dermal application.

In the rat the excretion of hydrocortisone aceponate was similar to that of hydrocortisone. The non-polar fractions extracted from urine and faeces were lower after topical application than after subcutaneous administration. Unchanged hydrocortisone aceponate was not detected in the urine or faeces following topical application but was detected in the urine following subcutaneous administration. A higher proportion of the dose was eliminated in faeces rather than urine. Total elimination was higher after subcutaneous administration than after topical application for both substances. The elimination half-lives for hydrocortisone and hydrocortisone aceponate were equivalent in urine and in faeces for both routes of administration.

Tissue distribution and dermal distribution following a single dermal application of hydrocortisone aceponate (ointment and cream) was compared to hydrocortisone butyrate cream and hydrocortisone acetate ointment in the guinea pig. The hydrocortisone aceponate ointment and the hydrocortisone butyrate cream penetrated the skin to a higher degree than the other products. For all products, tissue concentrations were higher at day 1 than day 7, with the higher radioactivity levels being found in the gastro-intestinal tract, the treated skin and the liver. Similar cumulative excretion profiles were seen for all products. The penetration of all products was similar in intact and scarified skin.

In a study in rabbits no difference was seen in plasma pharmacokinetics following a single topical application of hydrocortisone aceponate to intact or scarified skin.

Toxicological studies

Single dose toxicity

Hydrocortisone Aceponate

A total of 12 single dose toxicity studies carried out in 1979 with Retef (hydrocortisone aceponate) have been submitted as part of this dossier (see summary below). With the exception of the Magnusson & Kligman sensitisation test, all the studies were GLP compliant.

In these acute toxicity studies, hydrocortisone aceponate induced a variety of toxicity symptoms including sedation, ataxia, dyspnoea, cyanosis, mydriasis, lachrymal secretion, muscular hypotonia, decrease in food consumption and of bodyweight gain, vomiting and death.

In summary, hydrocortisone aceponate has a low acute toxicity profile after a single administration whatever the route considered.

For the oral route no acute toxic effects were observed at 1000 mg/kg in rats and mice and at 8000 mg/kg in dogs. For the intraperitoneal route no acute toxic effects were observed at 464 mg/kg in rats and mice and at 100 mg/kg in dogs. For the subcutaneous route no acute toxic effects were observed at 464 mg/kg in rats and at 681 mg/kg in mice and dogs. For the dermal route no acute toxic effects were observed at the highest dose tested (4000 mg/kg) in rats and mice.

Hydrocortisone aceponate formulation

Six recent GLP studies were performed using the hydrocortisone aceponate product according to the current OECD guidelines to determine the acute toxicity of the product and to estimate user safety.

No mortalities were recorded during the acute toxicity studies.

Oral Acute Toxicity:
Signs of ataxia, motor activity decrease, piloerection, respiratory troubles, ptosis and hypotonia were observed from 30minutes to the 3rd day after oral administration but no mortality was recorded. According to the globally harmonised system (GHS) for the classification of substances which cause acute toxicity, the hydrocortisone aceponate product was classified in Hazard Category 5 of unclassified with a LD_{50} and LD_0 higher than 2000 mg/kg in the rat.

Dermal Acute Toxicity:
According to the criteria defined by directive 67/548/EEC and its successive amendments, the hydrocortisone aceponate product was unclassified among the chemicals dangerous by contact with the skin in the rat.

Inhalation Acute Toxicity:
A decrease in motor activity and partial ptosis were observed from 1h to 4h of exposure in male and female rats. Mean bodyweight gain (day 15 - day 1) was 98.2 ± 10.7 g for the males and 26.2 ± 11.4g for the females. According to the criteria defined by directive 67/548/EEC and its successive amendments, the hydrocortisone aceponate product was not classified among the chemicals dangerous by inhalation in the rat.

Ocular Irritation:
In the acute eye irritation/corrosion test hydrocortisone aceponate was classified among the chemicals irritating to the eye (R36). One hour after the application of hydrocortisone aceponate the conjunctiva of all 3 rabbits were beefy red to diffuse crimson in colour with slight to obvious chemosis and the iris was congested. After 24h these reactions were still visible and a partial corneal opacity was observed. At 72h after administration the irritative reactions were diminished and complete reversibility was observed 9 days after application.

Dermal Irritation:
In the acute dermal irritation/corrosion test hydrocortisone aceponate was not classified among the chemicals irritating to skin. One hour after application there was a slight erythema in all three animals. This reaction was still present in 2 of the animals after 24h but was not observed at 48h or 72h.

Sensitisation Test:
One control animal (n=10) and one treated animal (n=20) developed a discrete or patchy erythema at the site of the challenge exposure. Products are sensitisers if there is a reaction in 15% of the treated animals. Therefore 184.02 was not considered a product which may cause sensitisation by skin contact.

Studies were carried out according to current OECD guidelines and the conclusions were justified. The hydrocortisone aceponate product was identified as an ocular irritant and the manufacturer has included warnings of this in the SPC.

Overall, the observed toxicity symptoms were typical for glucocorticoid toxicity. Signs of toxicity were observed at lower doses for the subcutaneous and peritoneal route compared to the oral route. No systemic signs of toxicity were recorded following dermal administration of 4000 mg/kg hydrocortisone aceponate.
The hydrocortisone aceponate product was not considered harmful via oral, dermal or inhalation administration, nor was it a dermal irritant and does not appear to be a sensitising agent (Buehler test). It was, however, an ocular irritant and warnings to this effect are included in the SPC.

Repeated dose toxicity

The changes observed during 8 repeated dose toxicity studies in different species were related to its glucocorticoid activity. The principal organs of toxicity were stomach, lungs, spleen, thymus, adrenals, pituitary, kidney and liver. Subconjunctival administration was the most sensitive route tested in repeated dose toxicity studies with a NOEL of 0.127 mg hydrocortisone aceponate per day (in hydrophilic cream) being identified in rabbits and rats. Subcutaneous and cutaneous administration resulted in similar NOELs (0.33 mg and 0.3175 mg hydrocortisone aceponate per kg bodyweight per day, respectively, in rabbits). At doses above the NOEL, chronic toxicity was weaker by the cutaneous route compared to the subcutaneous route, indicated by a marked reduction in the magnitude of findings for cutaneous compared to subcutaneous administration. No difference in NOEL was recorded for abraded or intact skin.

Aqueous hydroxypropyl methylcellulose gel, cream or ointment vehicles were used in the repeated dose toxicity studies.

Reproductive toxicity, including teratogenicity

According to Annex I of Directive 2001/82/EC as amended by 2004/28/EC, it is not required to conduct studies on the effects on reproductive toxicity when the systemic absorption of a topical treatment is negligible. This criteria was fulfilled since the bioavailability of hydrocortisone aceponate in the target species was estimated to be 0.2% after 7 days of cutaneous application of the hydrocortisone aceponate product at the intended therapeutic dose.

A series of 4 older studies examining the reproductive toxicity of hydrocortisone aceponate was provided. Embryotoxic and teratogenic effects of hydrocortisone aceponate, including skeletal changes, reduction in foetal and placental weight and elevated post-implantation losses, were seen in rats and rabbits at higher doses. No effects were seen on the length of gestation in either species. A reduction in the survival of the resulting offspring was also observed.

The lowest NOELs for reproductive toxicity were in the rabbit during the organogenesis period where embryotoxic effects were seen at 0.33 mg/kg (NOEL 0.1 mg/kg).

No studies of reproductive toxicity in the target species were provided. As a consequence of this the applicant has included a warning regarding the use of Cortavance in pregnant animals in the SPC.

Mutagenicity

Five mutagenicity studies were provided all of which showed that hydrocortisone aceponate tested up to cytotoxic levels did not reveal any indication of mutagenic properties with respect to chromosomal or chromatid damages in human peripheral lymphocytes with or without metabolic activation.

Carcinogenicity (if necessary)

No long term carcinogenicity studies were performed with hydrocortisone aceponate because no evidence of mutagenic potential was evident in the mutagenicity testing.

Studies of other effects

Special studies

The main organs of toxicity were well studied in the repeated toxicity studies.

The principal organs of toxicity were the stomach, lungs, the spleen, the thymus, adrenal, pituitary, kidney and liver. For example, increased weight and fatty degeneration of the liver and kidney were often seen as far as spleen and thymus atrophies.

All organs were previously identified as potential targets for glucocorticoid related toxicity.

Observations in humans

Two studies carried out in humans have been included in the dossier.

It was concluded from these two studies that the activity of hydrocortisone aceponate cream and ointment (Retef) was equivalent to that of reference preparations containing triamcinolone acetonide, fluocortolone monohydrate, betamethasone 17-valerate or hydrocortisone 17-butyrate and that hydrocortisone aceponate was well tolerated applied cutaneously at a maximum dose of 25.4mg on the lesion area twice daily (max 50.8 mg/child/day) in children with dermatitis.

Microbiological studies (studies on human gut flora and organisms used in food processing)

Hydrocortisone aceponate belongs to a class of molecule devoid of any microbiological activity. Furthermore, Cortavance is only intended to be used on dogs.

User Safety

User safety has been assessed by the applicant according to guideline EMEA/CVMP/543/03.

Inherent Toxicity

The toxicity of the test product and the active ingredient, hydrocortisone aceponate, has been studied for different routes of administration in a number of animal models.

Exposure of the user

The manufacturer has identified 7 risks situation associated with Cortavance. They were:

- In the pre-application phase
    1. Storage by a professional user
    2. Storage by a non-professional user
    3. Opening and accessing product by non-professional user
    4. Screwing the pump spray onto the flask by non-professional user
- In the application phase
    5. Application by the professional user
    6. Application by the non-professional user
- In the post-application phase
    7. Stroking the dog or handling the dog fur by the non-professional user

For this product professional users are almost exclusively the prescribing veterinarians, while the non-professional users include the dog's owner and the family of this person.

A thorough description of the risk scenarios and exposure assessments were presented.

Since the product is distributed as a Prescription Only Medicine, the professional users who prescribe the product should inform the pet owner on the product method of use, the risk linked to the product and on the precautions of use.

The exposure of the professional user is limited to product storage in the pre-application phase and to demonstration of the product in the application phase.

The following risk control options were taken for the product:

- Restriction of distribution. The product is a prescription only medicine.

- Restriction of Application method. The product is a spray delivering a small volume. In contrast to dermocorticoid creams or ointment products no hand contact or massage is necessary for application.

- Restriction of field of use. The product is to be used in a ventilated room and far from a naked flame.

- Packaging. A reduced pack size of 76mL will be used.

The following warnings and safety measures will inform the professional and non-professional users on the SPC and package.

Concerned Risks	SPC warning
Accidental eye contact	Avoid contact with the eyes. In case of accidental contact, rinse with abundant quantities of water. In case of eye irritation, seek medical attention.
Excipient flammability	Flammable. Do not spray on naked flame or any incandescent material. Do not smoke while handling the product. Spray preferably in a well ventilated area. (Warning symbol to be included)
Accidental ingestion	In the event of accidental ingestion, seek medical advice and show the leaflet or the label to the physician.
Accidental skin contact	In case of accidental skin contact, it is recommended to wash thoroughly with water. Wash hands after use.
Risks for children	Keep out of reach and sight of children

The suggested warnings are appropriate and complete.

A thorough and satisfactory description of the risk scenarios and exposure assessments were presented.

Environmental Risk Assessment

Phase I Assessment

According to the Phase 1 decision tree of the CVMP/VICH/592/98 guideline, the decision is made to stop in phase 1, since the product is not to be used in food-producing animals. Accordingly there is no need for further investigation of the ecotoxicity of the product and no additional data have been supplied regarding the ecotoxicity of the product.

Phase II Assessment

Not Applicable.

Conclusion:
Due to the anticipated limited use of this product in a non-food producing animal there is no requirement for the conduct of a detailed environmental risk assessment.

Residue documentation

Not Applicable

CLINICAL ASSESSMENT (EFFICACY)

PRECLINICAL STUDIES

Pharmacodynamics
Pharmacological class: Glucorticosteroid, dermatological preparation.

In vitro activity of HCA
Neither spasmolytic nor spasmogenic properties were detected of hydrocortisone aceponate in an isolated guinea pig ileum model using histamine, acetylcholine and barium chloride to induce contractions. No oxytocic properties for hydrocortisone aceponate were observed up to $1*10^{-3}$ g/mL in an *in vitro* rat uterus assay. Dose-dependent tocolytic effects (ED_{50} $3*10^{-4}$ g/mL) were observed.

In vivo activity of HCA
Preventive topical administration of hydrocortisone conditioner for 3 days slightly decreased wheal size in the skin of dogs challenged with intradermal injection with rabbit anti-canine IgE polyclonal antibodies compared to untreated controls, but did not affect erythematous flares nor the IgE-mediated late-phase reactions measured as dermal thickness, eosinophil counts and number of dermal CD3-positive T lymphocytes.

Skin-blanching (a result of vasoconstriction) tests in healthy human volunteers revealed higher potency of hydrocortisone aceponate compared to prednicarbate when applied un-occluded. An ultra-violet erythema test did not reveal significant difference between hydrocortisone aceponate and prednicarbate. However, due to lack of atrophogen (reduction of skin thickness) potential of hydrocortisone aceponate, the calculated benefit (glucocorticoid effect)/risk (skin thickness reduction potential) ratio for this substance was equal to that of prednicarbate and superior to that of betamethasone 17-valerate. Skin-blanching tests in healthy human volunteers exposed topically for 16 hours prior to challenge revealed significant effect of two hydrocortisone aceponate formulations; Retef cream and Retef ointment compared to placebo and hydrocortisone 21-acetate, whereas comparison to other topical glucocorticoid products (including betamethasone 17-valerate, hydrocortisone 17-byturate and fluocortolone monohydrate) revealed no differences.

In a granuloma pouch test in rats using croton oil as a subcutaneous irritant, Retef (in 0.8% hydroxypropyl-methylcellulose gel) was found to significantly decrease the produced amount of exudates when administered PO with an ED_{50} of approximately 10 mg/kg.

Subcutaneous administration of a hydrocortisone aceponate formulation (Retef in 0.8% hydroxypropyl-methylcellulose gel) to male NMRI-mice for 5 days (0.001, 0.01, 0.10, 1.0, 10.0 and 50.0 mg/kg bw/day) resulted in a dose-related decrease in thymus weight with an ED_{50} of 18.0 mg/kg SC. For comparison, ED_{50} for a positive control (hydrocortisone acetate) was 12.0 mg/kg.

Oral administration of HCA (vehicle 0.8% hydroxypropyl-methylcellulose gel) at 1000 and 1470 mg/kg bw to male NMRI mice did not reveal any anti-convulsive properties of the formulation in an electroshock-induced convulsion model.

No effect on spontaneous motility was observed in male NMRI mice administered HCA (vehicle 0.8% hydroxypropyl-methylcellulose gel) orally at 464 and 681 mg/kg bw.

Hexobarbitone-sleeping time in mice was prolonged by 11% after oral administration of 215 mg HCA (vehicle 0.8% hydroxypropyl-methylcellulose gel)/kg bw, by 42%af 316 mg/kg and by 92% at 464 mg/kg.

No anti-nociceptive properties of HCA (vehicle 0.8% hydroxypropyl-methylcellulose gel) administered orally (up to 681 mg/kg bw) were observed in a writhing test (induction using acetic acid IP) in mice.

Administration of HCA in propandiol to anaesthetised mature mongrel dogs resulted in changes in cardiac output (23% decrease) and heart rate (19% increase) at 1.0 mg/kg bw IV. Doses of 0.100 and 0.316 mg/kg IV induced slight dose-independent changes.

No local anaesthetic effect of 2.5 and 5% HCA (vehicle 0.8% hydroxypropyl-methylcellulose gel) was detected after conjunctival administration to rabbits.

In vitro models demonstrated no antagonistic/agonistic properties of hydrocortisone aceponate (HCA) regarding histamine, acetylcholine and barium chloride induced contractions. No oxytocic activity of HCA was observed, whereas tocolytic effects were described (ED50 $3*10^{-4}$ g/mL).

Hydrocortisone aceponate has been demonstrated to have dose-dependent anti-inflammatory effect (reduction of oedema and exudate formation) in various *in vivo* models. Anti-allergic effect was demonstrated in one *in vivo* study (DNCB-induced delayed hypersensitivity), whereas other studies showed no anti-allergic effect in the chosen models.

No evidence of anti-convulsive, anti-nociceptive or local anaesthetic effects were found, whereas decreases in thymus weight (EC50 18 mg/kg SC), increase in hexobarbital-induced sleeping time (range 215 to 464 mg/kg PO) and slight effects on cardiovascular parameters (0.100 and 0.316 mg/kg IV) were described in different studies. At 1.0 mg/kg IV more pronounced effects on cardiac output and heart rate were seen.

Two GLP-compliant pharmacokinetic studies in dogs showed that radiolabelled HCA penetrates intact clipped skin when applied according to recommendations. After one application, radioactivity was quantifiable in blood from 4 hours after administration and levels increased until the end of observation (48 hours). Repeated dermal applications for 7 consecutive days resulted in quantifiable levels in blood after 4 or 8 hours with a mean C_{max} of 17.96 ng eq/g. Maximum serum concentrations were reached approximately 10 days after termination of treatment (at 414 hours). Thirty-four days after cessation of exposure, mean blood level was 6.35 ng eq/g. An estimated $t_{½}$ was 267 hours (~11 days) and thus a prolonged systemic exposure can be anticipated when using the product according to recommendations.

The last pharmacokinetic study in two dogs demonstrated that when treating according to label, 1 to 2 % of the total dose can be expected to be in free form on the skin at 30 minutes to 4 hours post-application.

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The final pharmacokinetic study in two dogs demonstrated that when treating according to label, 1 to 2 % of the total dose can be expected to be in free form at 30 minutes to 4 hours post-application.

Two GLP-compliant tolerance studies have been performed in dog applying 1X, 3X and 5X the recommended dose topically on clipped skin for twice the recommended duration (14 days) on an area

of approximately 1/3 of skin surface (~1500 cm^2). Slight erythema was observed in 15/24 animals treated with Cortavance in one study; this was not dose-dependent and thus may be attributed to the vehicle. These findings are not regarded as a major clinical concern. More important changes attributable to the product are inhibition of the adrenal-pituitary axis (expressed as decreased ACTH and cortisol plasma levels, decreased cortisol-releasing capacity upon ACTH-stimulation and decreased adrenal weights) and possibly immunosuppression (decreased lymphocyte count and decreased axillary lymph node weight) at 3X and 5X dosing for twice the recommended duration of treatment and 1500 cm^2 treated area. Minimum capacity upon ACTH-stimulation was seen at Day 21 (3X) and Day 35 (5X) with ACTH-stimulated cortisol levels less than 10% of that of control dogs. Recovery was achieved at 9 and 11 weeks after initiation of treatment. This implies a reduced capacity to handle stress for a prolonged period after treatment. Thus care should be taken to avoid overdosing and this was clearly addressed in the SPC.

CLINICAL STUDIES

Laboratory trials

The Applicant submitted one pilot efficacy study using a dog flea allergy dermatitis model examining the effects of a product claimed to be Cortavance. However, as the product contained cetiol and dosing was 300 µL/cm^2, this was not the original Cortavance and not the recommended dose of 260 µL/100 cm^2. Concentration was presented as 0.0635% (presumably w/w). Hence, conclusions should be considered as indicative only of HCA efficacy and not of Cortavance specifically. The study demonstrated a significant effect of the HCA-containing spray when applied once daily at 300 µL/100 cm^2 skin for 7 days on the two primary response variables flea allergy dermatitis index (FAD index) and the total duration of pruritus. It thus appears that HCA has an anti-inflammatory effect both in decreasing the extent of clinical lesions of the skin and by relieving symptoms of flea allergy dermatitis in dogs.

Dose determination

The Applicant provided a GCP-compliant dose determination study using an experimental canine flea allergy dermatitis model. Significant reduction of the clinical score of lesions (FAD score) was seen at dosage levels similar to or twice the recommended. No further reduction was seen at the 2X dose and consequently the choice of dose appears reasonable. Significant reduction was not achieved before Day 7 of treatment, thus supporting a 7 day duration of treatment. All though the applicant concluded that total time of pruritic events was reduced 5-fold, this was not a statistically significant finding and no significant differences were detected in connection to pruritus parameters. Hence, this study did not support an anti-pruritic effect of the product

Dose confirmation

The Applicant provided a GLP-compliant dose confirmation study using an experimental canine flea allergy dermatitis model using Cortavance according to proposed use. Significant reduction of clinical lesions (assessed by FAD score) was confirmed for Cortavance. It was concluded that no significant effect on pruritus parameters was seen because groups were not balanced in regard of pre-treatment pruritus. However, statistical models should be able to identify an effect even though initial values differ between groups for example by pairing data. Furthermore, the dose determination study did not detect a significant anti-pruritic effect despite pre-treatment pruritus-values being similar across groups. In addition, the above mentioned pilot study demonstrated a significant reduction in pruritus duration despite large difference between mean pre-treatment pruritus duration. Consequently, this study does not confirm an anti-pruritic effect of Cortavance.

The Applicant provided a further GLP-compliant efficacy study using Cortavance according to recommendations in an experimental canine flea allergy dermatitis model. Significant reduction was observed in clinical lesion score (FAD score) on Day 2 and 7 of treatment as well as the number and duration of pruritic events. Thus, this study confirms an effect of Cortavance on both inflammation and pruritus in dogs allergic to fleas. In contrast to the previous dose determination and confirmation studies, a significant reduction was observed in pruritus parameters. This may be related to the fact that the dogs in this study received flea treatment, which was not the case in previous studies. This was reflected in the SPC of Cortavance.

Field trial

Evaluation of the therapeutic efficacy of Cortavance in the treatment of pruritic dermatitis in the dog

The Applicant also submitted the results of a multicentre, controlled and randomised GCP-compliant study conducted in 2004-2005 in 19 veterinary practices in France (14 sites) and Belgium) (5 sites). The objective of the study was to assess field therapeutic efficacy of Cortavance in the treatment of pruritic dermatitis in dogs and to confirm safety of the test product under field conditions.

Animals: One-hundred and five dogs (40M, 65F) of a total of 115, body weight 2 to 51 kg (mean 18.2±13.3 kg), age 0.5 to 14 years (mean 6.6±3.7 years). Thirty-three different breeds including cross-breeds were included.

Inclusion criteria: Patients presented to veterinary consultation with pruritic dermatitis characterised by pruritic skin inflammation without clinical signs of bacterial, fungal, or parasitic infection (other than fleas). Animals with flea allergy dermatitis could be included.

Dogs were either allocated to treatment with hydrocortisone aceponate spray or a positive control, with a comparator product (active ingredients: prednisolone acetate (0.125 g), hexetidine (0.150 g), and benzocaine (2 g) in 100 mL) : 54 (18M, 36F) were treated with Cortavance spray and 51 (22M, 29F) were treated with the comparator product spray.

Cortavance spray was administered topically at the dosage of 260 µL/100 cm² of injured skin, once daily for 7 days. The comparator product spray was administered topically at the dosage of 1 pressure for 60 cm² of injured skin twice daily for 7 days.

Clinical examinations were performed on Day 0, Day 7, and Day14. Pruritus was scored at each time of examination from 0 (=normal) to 3 (=severe sign). Score of pruritus (SP) was the primary response parameter. Skin lesions were scored at each time of examination from 0 (=normal) to 3 (=severe sign). These scores concerned erythema, papules/pustules, erosions/excoriations, lichenification/hyperpigmentation, extent of lesions and were added to obtain a score of lesions (SL).

The primary response variable was the clinical recovery rate. Percentages of clinical recoveries, failures and improvements were calculated for each group for Day 0 to Day 7. Clinical recovery was defined by disappearing of signs of pruritus (score 0) at the end of treatment (Day 7). Failure was defined as stagnation or deterioration of pruritus during the treatment period, or if a new treatment was administered before or on Day 7. Improvement was defined as absence of recovery with a decrease of score of pruritus at the end of treatment compared with pre-treatment score.

The secondary efficacy criteria were the percentage of SP reduction on Day 7, the percentage of SL reduction on Day 7 and the percentage of clinical relapses - clinical relapse was defined as reappearance of clinical signs of pruritus between Day 7 and Day 14 or the set up of a new treatment between Day 7 and 14.
Any adverse effect observed by the owner was documented and decision on actions taken were made by the investigator.

Results demonstrated no significant difference between the percentages of dogs with clinical recovery at Day 7 treated with Dortavance spray (50%) or with the comparator product spray (51%). The clinical signs were improved in 42.6% and 35.3% of dogs in the Cortavance and comparator product groups respectively. Eleven clinical failures were observed: 4 (7.4%) in the Cortavance group and 7 (13.7%) in the comparator product group. There was no statistically significant difference between groups.

Forty-eight animals (88.9%) Cortavance-treated and 38 (74.5%) comparator product-treated presented a percentage of SP reduction ≥50%.

Forty-two (77.8%) Cortavance-treated and 30 (58.8%) comparator product-treated dogs presented a percentage of SL reduction ≥50.
One dog in each group presented deterioration of skin lesions on Day 7; one Cortavance-treated and 2 comparator product-treated presented no reduction of SL.

Aggravated lesions was reported in one dog between Day 1 and Day 4 (just after application the dog wept and attempted to lick the treated zone and erythema was more pronounced). On Day 7 these signs had disappeared as assessed by the veterinarian investigator.
Concurrent treatments unrelated to the skin disorder of dogs completing the study included: clomipramine hydrochloride (one dog), enalapril and furosemide (one dog), vaccination (two dogs)

Conclusion:
In a GCP-compliant field trial comparing efficacy of Cortavance (n=54) to that of a prednisolone acetate-containing registered product in the treatment of pruritic dermatitis without signs of concurrent infection (other than fleas) in dogs Cortavance showed efficacy comparable to that of the comnparator product regarding the parameters clinical recovery rate, improvement and failure, mean score of pruritus, mean score of lesions and number of clinical relapses.

BENEFIT RISK ASSESSMENT

Hydrocortisone aceponate belongs to the diester class of corticosteroids possessing potent intrinsic glucocorticoid activity. The product Cortavance is formulated as a spray intended for topical dermatological treatment containing 0.0584 mg hydrocortisone aceponate/100 mL. The proposed dosage regimen is two pump spray activations once daily on an area of approximately 10 cm x10 cm (equalling 1.52 µg HCA/cm^2) for 7 consecutive days.

The data provided within Part II are generally not extensive, but is in compliance with the current guidelines. The composition of the above product is adequately described.

The product complies with the TSE Note for Guidance (EMEA/410/01 Rev.2.) and Council Directive 2001/82/EC, as amended.

The pharmacokinetics of hydrocortisone aceponate were similar to those of hydrocortisone in rats and rabbits. Following subcutaneous or topical administration, the highest drug concentrations were measured in the gastro-intestinal tract, the liver and the kidneys. No difference in pharmacokinetics was seen in animals with abraded or intact skin.

The observed toxicity symptoms were typical for glucocorticoid toxicity. Signs of toxicity were observed at lower doses for the subcutaneous and peritoneal route compared to the oral route. No systemic signs of toxicity were recorded following dermal administration of 4000 mg/kg hydrocortisone aceponate. Cortavance was not considered harmful via oral, dermal or inhalation administration, nor was it a dermal irritant and does not appear to be a sensitising agent (Buehler test). It was, however, an ocular irritant.

Subconjunctival administration was the most sensitive route tested in repeated dose toxicity studies with a NOEL of 0.127 mg hydrocortisone aceponate per day (in hydrophilic cream) being identified in rabbits and rats. Subcutaneous and cutaneous administration resulted in similar NOELs (0.33 mg and 0.3175 mg hydrocortisone aceponate per kg bodyweight per day, respectively, in rabbits). At doses above the NOEL, chronic toxicity was weaker by the cutaneous route compared to the subcutaneous route, indicated by a marked reduction in the magnitude of findings for cutaneous compared to subcutaneous administration. No difference in NOEL was recorded for abraded or intact skin.

The applicant included a series of older studies examining the reproductive toxicity of hydrocortisone aceponate. Embryotoxic and teratogenic effects of hydrocortisone aceponate, including skeletal changes, reduction in foetal and placental weight and elevated post-implantation losses, were seen in rats and rabbits at higher doses. No effects were seen on the length of gestation in either species. A reduction in the survival of the resulting offspring was also observed.

No evidence of mutagenicity was identified in a series of studies conducted according to the relevant guidelines.

In a study of children with dermatitis, hydrocortisone aceponate was effective and well tolerated at topical doses of up to 50.8 mg/child/day. Burning was observed in one of 16 children (6%) and one child discontinued treatment due to lack of efficacy.

User safety has been assessed according to guideline EMEA/CVMP/543/03. A thorough description of the risk scenarios and exposure assessments are presented. The suggested warnings are appropriate and complete.

Due to the anticipated limited use of this product in a non-food producing animal there is no requirement for the conduct of a detailed environmental risk assessment.

In vitro models demonstrated no antagonistic/agonistic properties of hydrocortisone aceponate regarding histamine, acetylcholine and barium chloride induced contractions. No oxytocic activity of hydrocortisone aceponate was observed, whereas tocolytic effects were described (ED50 $3*10^{-4}$ g/mL).

Hydrocortisone aceponate was demonstrated to have dose-dependent anti-inflammatory effect (reduction of oedema and exudate formation) in various *in vivo* models. Anti-allergic effect was demonstrated in one *in vivo* study (DNCB-induced delayed hypersensitivity), whereas other studies showed no anti-allergic effect in the chosen models.

No evidence of anti-convulsive, anti-nociceptive or local anaesthetic effects were found, whereas decreases in thymus weight (EC50 18 mg/kg SC), increase in hexobarbital-induced sleeping time (range 215 to 464 mg/kg PO) and slight effects on cardiovascular parameters (0.100 and 0.316 mg/kg IV) were described in different studies. At 1.0 mg/kg IV more pronounced effects on cardiac output and heart rate were seen.

Two GLP-compliant pharmacokinetic studies in dogs showed that radiolabelled HCA penetrates intact clipped skin when applied according to recommendations. After one application, radioactivity was quantifiable in blood from 4 hours after administration and levels increased until the end of observation (48 hours). Repeated dermal applications for 7 consecutive days resulted in quantifiable levels in blood after 4 or 8 hours. Maximum serum concentrations were reached approximately 10 days after termination of treatment and labelled material was still present in blood 34 days after cessation of exposure. Thus a prolonged systemic exposure can be anticipated when using the product according to recommendations.

A pharmacokinetic study in two dogs demonstrated that when treating according to label, 1 to 2 % of the total dose can be expected to be in free form on the skin at 30 minutes to 4 hours post-application.

Two GLP-compliant tolerance studies were performed in dog applying 1X, 3X and 5X the recommended dose topically on clipped skin for twice the recommended duration (14 days) on an area of approximately 1/3 of skin surface (~1500 cm^2). Slight erythema was observed in 15/24 animals treated with Cortavance in one study; this was not dose-dependent and thus may be attributed to the vehicle. Cutaneous application of 184.02 inhibited the adrenal-pituitary axis (expressed as decreased ACTH and cortisol plasma levels, decreased cortisol-releasing capacity upon ACTH-stimulation and decreased adrenal weights) in 3X and 5X dosed animals for twice the recommended duration of treatment and 1500 cm^2 treated area and caused immunosuppression (decreased lymphocyte count and decreased axillary lymph node weight) in the 5X group. Minimum capacity upon ACTH-stimulation was seen at Day 21 (3X) and Day 35 (5X) with ACTH-stimulated cortisol levels less than 10% of that of control dogs. Recovery was achieved at 9 and 11 weeks after initiation of treatment. This implies a reduced capacity to handle stress for a prolonged period after treatment. Thus care should be taken to avoid overdosing and this was consequently clearly addressed in the SPC.

The clinical part of the dossier consisted of one pilot and one actual efficacy study, one dose determination study, one dose confirmation study and one field trial.

Dose determination and confirmation studies generally supported the chosen dose of 1.52 µg/cm^2 skin and the duration of treatment of 7 days. Significant reduction of clinical lesions was demonstrated in several studies using a canine flea allergy dermatitis model, whereas significant reduction of pruritus was demonstrated in only one of these laboratory studies, where animals were concurrently treated with an ectoparasiticide. Thus an addition to the SPC specifically recommending flea treatment together with treatment of flea allergy dermatitis with Cortavance was appropriate.

The field trial consisted of a multi-site study comparing treatment with Cortavance with a prednisolone acetate-containing product of canine patients with pruritic dermatitis characterised by skin inflammation without signs of infection (except fleas). Fifty-four dogs were treated with Cortavance and 51 with the comparator product. Results indicated comparable efficacy between the two products.

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EC as amended.