10 September 2015
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Zycortal (EMEA/V/C/003782/0000)

International non-proprietary name: desoxycortone

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

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Introduction

On 17 April 2014, the applicant Dechra Limited submitted an application for a marketing authorisation to the European Medicines Agency (The Agency) for Zycortal 25 mg/ml prolonged-release suspension for injection, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No. 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 14–16 May 2013 as Zycortal contains a new active substance, desoxycortone (as desoxycortone pivalate), which was not authorised in the Community on the date of entry into force of the Regulation.

The rapporteur appointed was Helen Jukes and co-rapporteur Hanne Bergendahl.

The applicant applied for the following indication: "For use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease)."

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Zycortal prolonged-release suspension for injection contains 25 mg/ml desoxycortone pivalate and is presented in multidose glass vials containing 4 ml. The route of administration is subcutaneous use.

The CVMP adopted an opinion and CVMP assessment report on 10 September 2015.

On 6 November 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Zycortal.

Scientific advice

Not applicable.

MUMS/limited market status

The applicant requested MUMS/limited market classification for this product/application by the CVMP, and at their April 2013 meeting the Committee confirmed that, where appropriate, the data requirements in the appropriate CVMP guidelines on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted for the following reasons:

- The prevalence of Addison's disease in dogs was considered low and therefore this product was considered a MUMS/limited market for the treatment of mineralocorticoid deficiency in dogs with primary adrenocortical insufficiency.
- No alternative veterinary medicinal product authorised for the target species for the same indication could be identified.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system 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 event occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance, desoxycortone pivalate, is manufactured and micronised in the European Union (EU). The ASMF procedure is followed.

The manufacturer responsible for batch release of the finished product is Dales Pharmaceuticals (Skipton, UK). A manufacturing authorisation was issued on 5 August 2013 by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and this confirms that the site is authorised for the manufacture and batch release of sterile veterinary medicinal products. A certificate of GMP compliance, dated 7 April 2014 issued by MHRA, was provided based upon an inspection carried out on 20 January 2014.

The certificate of GMP compliance for the site of micronisation states that this site meets the GMP requirements for active substances. This is acceptable since micronisation is a step in manufacture of the active substance.

The Qualified Person (QP) of the manufacturer responsible for batch release of the finished product (Dales Pharmaceuticals) has provided a declaration that the manufacturer of the desoxycortone pivalate operates in compliance with the current guidelines on Good Manufacturing Practice for starting materials. This declaration is based on an audit of the manufacturing site.

No concerns have been raised during the assessment that would give rise to any manufacturing site inspection prior to authorisation.

Overall conclusions on administrative particulars

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

The GMP status and manufacturing authorisation for both the active substance and dosage form manufacturing sites have been satisfactorily established and are in line with legal requirements.

The CVMP guidelines on minor use minor species (MUMS) data requirements have been applied when assessing this application.

Part 2 – Quality

Composition

Zycortal 25 mg/ml prolonged-release suspension for injection is an opaque, white, sterile aqueous suspension for subcutaneous injection containing 25 mg desoxycortone pivalate per ml (equivalent to 19.9 mg/ml desoxycortone).

Although strength is normally expressed in terms of the active moiety (in this case desoxycortone), an almost identical product has been authorised in third countries for many years with the strength expressed in terms of the salt, that is, 25 mg/ml desoxycortone pivalate. It was therefore considered acceptable that the strength of this product is expressed in the same manner.

The content of the preservative, chlorocresol, in this multidose aqueous injection has been justified. Antimicrobial preservative efficacy studies have shown that the optimum concentration of chlorocresol in this formulation is 0.1% w/v.

Methylcellulose, sodium carboxymethylcellulose, polysorbate 60, sodium chloride and water for injections are included in the formulation.

Container

The primary packaging is a multidose Type I clear glass vial (8 ml capacity) sealed with a 20 mm grey Flurotec coated rubber stopper and 20 mm flip off aluminium seal. The fill volume of the suspension is 4 ml.

The immediate packaging conforms with the relevant European Pharmacopoeia (Ph. Eur.) and EC requirements.

The use of clear glass has been justified as the product has been demonstrated not to be sensitive to light.

Secondary packaging consists of a cardboard carton (each containing a package leaflet).

Development pharmaceutics

A comprehensive report on development pharmaceutics is presented which indicates that the formulation, method of manufacture and testing have all been carefully selected and justified.

The initial dose is 2.2 mg/kg bodyweight (bw), equivalent to 1 ml per 11.5 kg bodyweight. For a small dog breed this dose could result in a dose volume of 0.25 ml or less. Appropriate instructions are included in the SPC and package leaflet (PL) to use appropriately graduated syringes, particularly for administering small volumes.

In view of the possibility of large numbers of doses being withdrawn from a vial, tests for fragmentation and self-sealing of the closure (after the potential maximum number of punctures) were carried out on freshly filled and aged samples of the product. The results confirmed the 4 ml pack size was acceptable.

The active substance, desoxycortone pivalate, is practically insoluble in water. The formulation is designed as a prolonged-release suspension. The applicant has developed a dissolution test for release and stability testing of the finished product, which is discriminating. All the excipients used are typical for such a prolonged-release injectable suspension product. 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 product is terminally sterilised by heating in an autoclave, using a standard cycle of 15 minutes at 121 ºC.

The product pH was set in accordance with the specification for pH in the United States Pharmacopoeia (USP) for desoxycortone pivalate suspension.

The results of freeze/thaw testing demonstrated that "Do not freeze" is justifiably included in the SPC and product literature.

The finished product complies with the VICH guideline GL18 Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients.

The formulation is essentially the same as that used in the clinical trials. The clinical trial batches were manufactured using a larger manufacturing overage of the preservative than is now proposed. However, these batches had almost the same chlorocresol assay at release, due to larger manufacturing losses, therefore this is acceptable.

The pharmaceutical development section is considered comprehensive.

The choice of the raw materials incorporated in the formulation is discussed and justified.

Method of manufacture

The manufacturing batch formula is provided for the commercial batch size.

The manufacturing process (including production equipment) has been described in sufficient detail, and all the critical steps in the process have been identified and controlled.

The manufacturing process comprises dissolving, dispersing and mixing ingredients to obtain the suspension.

In-process controls are adequately defined.

Validation data are provided for three full scale batches manufactured at the finished product manufacturing site using the procedure and the formula described above. During the process validation, the manufacturing method was found to be effective and reproducible in producing a product that complied with the acceptance criteria. The homogeneity of the active substance in the batches was confirmed by the results of the in-process active substance assays. Overall, the results demonstrate good reproducibility of the manufacturing procedure and provide assurance that the manufacturing procedure can be considered as validated. All control tests on the finished product met the release specification, proving that a sterile product of consistent and high quality can be obtained with the manufacturing process.

The manufacturing process is considered reliable and able to produce a consistent finished product.

Control of starting materials

Active substance

The information for the active substance is presented in an active substance master file (ASMF).

Desoxycortone pivalate is the subject of a monograph in the United States Pharmacopoeia.

The synthetic reaction scheme of the manufacturing process is included together with a narrative description of the process. The manufacturing process consists of four chemical transformations. Purification involves three treatments with different solvents.

The definition of the starting material and the extent of the described synthesis are considered acceptable. The micronisation process is described.

The structure is fully elucidated.

A comprehensive discussion regarding impurities is included.

The specification for the active substance is justified in that it is that of the USP, supplemented with appropriate tests and limits for residual solvents and related substances. Other test methods are standard pharmacopoeial methods.

Batch analysis data for three production scale batches are provided and all parameters comply with the active substance specification. The results demonstrate consistency from batch to batch.

The open part of the ASMF is considered fully satisfactory giving satisfactory detail of the methods of manufacture and control.

The closed (restricted) part of the ASMF gives satisfactory detail of the methods of manufacture and control.

Excipients

The excipients, methylcellulose, sodium carboxymethylcellulose, polysorbate 60, sodium chloride, chlorocresol and water for injections, are each tested according to the requirements of the current respective Ph. Eur. monograph. The specifications and certificates of analysis provided comply with the relevant requirements. All excipients have previously been used in veterinary medicinal products authorised within the Community.

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

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

Control tests on the finished product

The descriptions provided of the methods used for the control of the finished product and the specification limits are appropriate to control the quality of a suspension for injection and this finished product. Furthermore the specifications proposed at release and at the end of shelf life are in accordance with VICH GL39 Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances.

Appearance is controlled visually. Identification of desoxycortone pivalate is confirmed using FTIR spectroscopy. Assay of the active substance is by HPLC. Suitable limits for viscosity, pH and extractable volume are included. The assay and identification of the preservative (chlorocresol) is by HPLC with appropriate limits. A test for dissolution is also included. The applicant has justified the absence of a test for the particle size of the active substance and for related substances in the finished product. The test for sterility is in accordance with Ph. Eur. 2.6.1.

The analytical procedures have all been satisfactorily validated in accordance with VICH requirements.

The shelf life specification is similar to that applied at release with two exceptions. For viscosity, a reduced lower limit applies for shelf life purposes which is justified by the stability results presented. A reduced lower limit of the nominal chlorocresol content is also supported for shelf life purposes as the product was demonstrated to pass the Ph. Eur. requirements for preservative efficacy. The absence of tests and limits for related substances is justified.

Certificates of analysis have been provided for three production scale batches of the finished product manufactured at the site proposed for commercial manufacture. The batches were manufactured and tested in accordance with the methods described above. The batches are those for which process validation data are supplied. The results demonstrate compliance with the proposed release specification.

Stability

For the active substance, forced degradation data have been provided. samples from commercial batches have been stored in simulated commercial packs and in accordance with VICH GL3 on stability testing of new veterinary drug substances and medicinal products (CVMP/VICH/899/99 Rev.1) under real-time (25 °C/60% RH) and accelerated (40 °C/75% RH) conditions and tested against the stability-indicating tests in the active substance specification. The stability data support the proposed retest period proposed for the active substance stored in the commercial packaging (double polyethylene bags in aluminium drums) without any restriction on storage conditions.

Stability studies on the finished product were performed under both long term and accelerated conditions, on samples from three production-scale batches of the product in the vial proposed for marketing and in accordance with VICH GL3 on stability testing of new veterinary drug substances and medicinal products (CVMP/VICH/899/99 Rev.1). Samples were tested using the methods of the finished product specification. Results are currently available after 18 months storage at 30 °C/65% RH and 6 months storage at 40 °C/75% RH. Samples are on test at 25 °C/60% RH but have not been examined. The analytical procedures used are stability indicating.

Supporting data are provided for product manufactured at a site no longer intended for manufacture but using the same process. Here, stability testing has been carried out at 30 °C/65% RH on samples from three production scale batches of the product in the vial proposed for marketing. Samples were tested using the methods of the finished product specification. The analytical procedures used are stability indicating. Results are available after 36 months storage at 30 °C/65% RH. It is concluded that product manufactured at this first site is less homogenous than the more recent batches manufactured at the finished product manufacturing site. This lack of homogeneity has led to the variable assay levels and lack of correlation seen in these batches. The proposed shelf life of 3 years with the storage precautions of "Do not store above 30 °C." is accepted.

Freeze/thaw testing demonstrate that the warning "Do not freeze" is also required in the SPC and other product literature.

A photostability study was carried out using one batch of finished product. Exposure to light caused no adverse effects and no warning is therefore needed to protect the product from light.

In-use stability data are provided for three batches of the product, stored at 25 °C/60% RH in the vials proposed for marketing, and tested in accordance with the finished product specification. An in-use shelf life of 120 days is justified by the data. Freshly-prepared product is stable for 120 days after broaching. The data for older product manufactured in a different site are variable. One batch does not show the same degree of stability as the freshly-prepared product. This is attributed to the lack of homogeneity of the older batches. The second batch manufactured of older product shows acceptable in-use stability over the 120 day period.

Based on the available stability data, the shelf life, in-use shelf life and storage conditions as stated in the SPC (and other product information) are acceptable.

Overall conclusions on quality

Zycortal 25 mg/ml prolonged-release suspension for injection is a sterile suspension for subcutaneous injection containing 25 mg desoxycortone pivalate per ml. The composition has been justified. The product is packaged in a clear glass vial sealed with a rubber stopper. The product is terminally sterilised by heating in an autoclave, using a standard cycle. The formulation is almost exactly the same as that used for the clinical trials.

The manufacturing process is described. The results of process validation demonstrate good reproducibility of the manufacturing procedure and provide assurance that the manufacturing procedure is validated.

An ASMF is provided for the active substance desoxycortone pivalate, which is the subject of a monograph in the United States Pharmacopoeia. The methods of manufacture and control are suitably described and stability data provided support the retest interval proposed.

The excipients are standard pharmaceutical ingredients and all comply with the current requirements of the European Pharmacopoeia.

No material of animal origin is used in the manufacture of Zycortal.

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product. Analytical methods and their validation are adequately described. The relevant EU and VICH guidance and Ph. Eur. requirements are taken into account.

Certificates of analysis have been provided for three batches manufactured at the site proposed for commercial manufacture.

Suitable stability studies have been carried out, under both long term and accelerated conditions, according to current VICH guidelines. The stability data provided support a shelf life of 3 years when stored below 30 °C. Freeze/thaw testing demonstrate that the warning "Do not freeze" is also required in the SPC and other product literature. The in-use stability data presented justify an in-use shelf-life of 120 days.

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 the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Part 3 – Safety

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Very limited pharmacokinetic data have been provided of relevance for part 3, having been restricted to absorption and elimination parameters in the target species, dogs. Only blood and urine samples were analysed in the studies submitted (DOCP004, serum and urine; DOCP005, serum only), meaning that distribution to different body compartments and the metabolic profile have not been clearly elucidated.

The pharmacokinetic profile of desoxycortone pivalate (DOCP) is likely to be different from the other esters. However, very large doses would have been required to discern exogenous from endogenous substance and as such a specific pharmacokinetic (PK) study would not enhance the user safety assessment.

Toxicological studies

Single dose toxicity

Cross-reference is made to the data provided for the pharmacokinetics section (see part 4). Although no clinical signs were noted in the dogs used in the two PK studies, there was no post-mortem work performed on the dogs after the studies were completed, so no definitive conclusions can be made from these studies regarding the NO(A)EL.

In addition, a study in Wistar rats was provided. Five groups of 15 animals per gender were administered DOCP once (in saline vehicle), by subcutaneous injection, at levels of 0, 0.15, 0.6, 2.4 and 9.6 mg/kg bw. Ten animals of each sex in each group were sacrificed 2 weeks after administration of the test product; the remaining five animals of each sex per group were sacrificed 12 weeks after administration. Mortality, viability, clinical signs, body weight and food consumption, ophalmoscopic examination, clinical pathology, urinalysis, macroscopy at termination, sperm analysis, organ weights and histopathology were evaluated.

No evidence of any systemic toxicity was revealed at any dose tested; however, there were prolonged injection-site reactions in all test groups.

A NOEL of 9.6 mg/kg bw was determined, but because there were no adverse reactions in this, the highest dose tested, a true NOEL would probably have a higher value, although it is unknown how much higher.

Repeat dose toxicity

In order to address the repeat-dose toxicity requirements, the applicant submitted a 2-day oral mouse study (Ref 24; EBC/0003; Hynes, 2008), which was not suitable to draw any conclusions, and cross-reference was made to a target animal tolerance study from the published literature (Ref 25; Chow et al., 1993). In addition to this literature study, the applicant also provided a proprietary, GLP-compliant target animal safety study (DP300-TAS-01) which investigated repeat dosing over a period of 6 months (see part 4).

Chow et al conducted a target animal safety study in which doses of 0.0, 2.2, 6.6 and 11.0 mg/kg bw/day for three consecutive days were administered every month for 6 months; as the recommended dose is 2.2 mg DOCP/kg once every 25 days, this equates to approximately 0, 3, 9, and 15 times the therapeutic dose. The study was not conducted to GLP and does not conform to any of the OECD guidelines that may be followed for repeat-dose studies. No NOEL can be established due to the dosing regimen used in the study.

The data provided demonstrate that there are effects on various organ weights – particularly related to the reproductive organs in male dogs. These changes occurred even at the lowest non-control dose; no No Observed Adverse Effect Level (NOAEL) could be determined as the study was not designed for that purpose.

In particular, DOCP administration affected body weight gain (in males), urine volume, urine specific gravity, urine concentration of creatinine, water consumption, concentrations of serum potassium, sodium, and blood urea nitrogen (BUN), weights of the epididymides, testes, adrenal, thyroid, and parathyroid glands in males and weight of the kidneys in both sexes, but did not affect food consumption, survival, or any other organ system.

Most of the observed effects appeared to be related to the pharmacological action of DOC. Some related effects that can be predicted from the known pharmacology of mineralocorticoids (hypertension, metabolic alkalosis, hypocalcaemia) were not investigated in the study provided.

In addition to this literature study, the applicant also provided a proprietary, GLP target species safety study which investigated repeat dosing over a period of 6 months (see below).

According to Annex I of Directive 2001/82/EC, as amended, a repeat-dose study conducted in the target animal (e.g. target animal safety study) may be used in place of a standard 90-day study conducted in rodents, for products intended for non-food-producing species, such as this (the same requirement applies for MUMS applications). However, the studies submitted did not allow the identification of a NO(A)EL, nor were they conducted in accordance with OECD guidelines. The data provided in this section, although not allowing a NO(A)EL to be set, do point to the possibility of there being developmental toxicity and/or reproductive toxicity associated with this substance.

Toxicological data are required in order to derive a reference value (NO(A)EL) that can be used as the basis of the user safety assessment. It is considered that the potentially most harmful route of accidental exposure to the product would be via self-injection. The likely outcomes were investigated in the single-dose study conducted in rats (see above) and a developmental screening study, also conducted in rats (see below).

Tolerance in the target species of animal

In addition to the published target animal species study described above, a proprietary target animal species tolerance study has been provided which indicates that signs of toxicity are apparent even at the recommended therapeutic dose (in healthy animals). The study is fully assessed in part 4. With regard to the relevance of the study to the user safety assessment, no NO(A)EL could be determined, but signs of kidney injury (inflammation) and increases in heart and kidney weights were apparent in dogs, along with a possible indication of reproductive organ toxicity (decreased weight of ovaries).

Reproductive toxicity

The target species safety studies raised a concern in this regard (effects on testes, epididymides and ovaries). Due to the nature of the changes to the reproductive organs, there may also be effects on fertility and/or embryo-foetal development.

A study in Wistar rats was provided. The purpose of this study was to evaluate the potential toxic effects of DOCP when administered two or three times (two weeks apart) by subcutaneous injection to rats, and to evaluate the potential of the test substance to affect male and female reproductive performance, such as gonadal function, mating behaviour, conception, parturition and early postnatal development.

Parental, local, general systemic, reproduction (up to and including implantation) and developmental (from implantation onwards) endpoints were evaluated.

The subcutaneous route was selected as it is a possible route of human exposure during handling or use of the product. The dose levels for this screening test were 0.15, 0.6, 1.8 and 5.4 mg/kg bw.

The following observations and examinations were evaluated: mortality / viability, clinical signs (daily), functional observations and locomotor activity (end of treatment), body weight and food consumption (at least at weekly intervals), clinical pathology (end of treatment), macroscopy at termination, sperm analysis, organ weights and histopathology on a selection of tissues, and reproduction/developmental parameters, consisting of mating, fertility and conception indices, precoital time, number of corpora

lutea and implantation sites, gestation index and duration, parturition, maternal care, sex ratio and early postnatal pup development (mortality, clinical signs, body weights and macroscopy).

There was no clear evidence of toxicity at any dose tested in this study.

Based on the results of this rat study, a NOEL of 5.4 mg/kg bw was derived, but as this dose was the highest tested, the true NOEL would probably be higher; it is unknown how much higher.

Mutagenicity/genotoxicity

The standard battery of genotoxicity studies (Ames test, in vitro human lymphocyte test and in vivo mouse micronucleus test) has been provided and there are no indications of genotoxic potential from DOCP.

Carcinogenicity

No data have been provided; the lack of genotoxic potential or structural alerts occurring in the molecule DOCP indicate that no data are required; however, due to the lack of repeat-dose or chronic toxicity data, a final conclusion on carcinogenic potential cannot be made.

Studies of other effects

Standard tests of ocular and dermal irritation in rabbits have been provided that were conducted using the product to be marketed. The results indicate that the product is slightly irritating to both the skin and the eyes. A dermal sensitisation study (Local Lymph Node Assay) has also been provided, which was also conducted using the product to be marketed. There was no indication that the product would induce dermal sensitisation.

Human data

No reports have been received on adverse reactions following use of desoxycorticosterone in man to the US FDA Center for Drug Evaluation and Research (CDER) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the USA and UK, respectively (Stepper 2005, Ref 30; Matthissen 2013, Ref 31).

DOCP is authorised for veterinary use as 'Percorten-V' in the USA and Canada. From the CVM ADE Comprehensive Clinical Detail Report listing from the cumulative date range 01/01/1987 to 30/04/2013 (FDA's Center for Veterinary Medicine, 2013), only one adverse event was reported in humans. Ophthalmic administration caused 'eye(s)/lid irritation'. There was also one event from Canada reported, in 1973, related to 'pruritus, rash papular'.

A literature search was performed using a number of databases (i.e. Scopus, Biological Abstracts, Embase, Int. Pharmaceuticals Abstracts, Life Sciences Collection, and Medline), and publicly available databases such as PubMed and Google Scholar. The search did not reveal any further data for accidental human exposure.

The acetate salt of desoxycortone is authorised in France for the treatment of mineralocorticoid substitution in acute adrenal insufficiency in man at a dose of up to 20 mg/person/day, and no adverse drug reactions to this product have been reported in the literature.

User safety

A user safety assessment was provided in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The main hazards currently identified are related to the mineralocorticoid effects of DOC. Injury to heart, kidneys and reproductive effects were identified from the target species safety studies.

The applicant considered 3 exposure scenarios: dermal and ocular exposure during loading and disposal of the syringe and accidental self-injection by the veterinarian. For loading the syringe the applicant considered that the veterinarian would be exposed dermally to 1 drop (0.05 ml) of the product, and for disposal of a used syringe, 0.5% of the maximum injection volume (0.0176 ml). For accidental injection it was considered that the user might be exposed to 10% of the maximum injection volume in a 40 kg dog (0.352 ml).

Dermal and eye irritation studies conducted in the rabbit showed that DOCP was a minimal irritant to the rabbit eye and skin. For the quantitative risk characterisation, the applicant used the lowest dose tested of 2.2 mg/kg bw from the two target animal safety (TAS) studies.

Applicant's calculation of margins of exposures (MOEs) for DOCP Suspension:

Scenario	**Exposure route**	**Relevant LOEL**	**Reasonable Worst-Case Estimated Exposure**	**MOE**
1: Filling the syringe	Dermal	2.2 mg/kg bw	0.0208 mg/kg bw	105
2: Administration to the animal	Parenteral	2.2 mg/kg bw	0.147 mg/kg bw	15
3: Disposal of the packaging and unused product	Dermal	2.2 mg/kg bw	0.0073 mg/kg bw	301

It was stated that dermal exposure might occur on 25% of occasions when filling the syringe and throughout the dosing period for syringe disposal. Accidental self-injection is considered to be rare in a professional person.

The user safety warnings proposed by the applicant for the SPC are:

- Avoid contact with the eyes and skin. In case of accidental spillage onto skin or eye, wash the affected area with water. If irritation occurs, seek medical advice immediately and show the package leaflet or the label to the physician.
- The veterinary medicinal product should not be administered by pregnant women.
- The safety of the veterinary medicinal product has not been established during pregnancy or lactation.
- In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician.

Although desoxycortone is authorised for the treatment of mineralocorticoid deficiency in man, it is noted that the acetate salt will have a different pharmacokinetic profile to the pivalate salt and it is also not sound to extrapolate a margin of safety from use in humans suffering from an endocrine insufficiency to healthy humans.

The toxicological point of departure identified by the applicant (2.2 mg/kg bw – the therapeutic dose in dogs) is derived from a target animal safety study, which did not conform to either OECD single-dose or

repeat-dose study designs, and it is the lowest dose tested in dogs, rather than a LOEL. In this case a MOE < 1000 would generally be considered inadequate to ensure the safety of the user. The CVMP accepted the 'NOEL' from the reproductive screening study in rats (5.4 mg/kg bw) since the frequency of injection was more representative of what might happen if someone were to accidentally inject themselves with the product, but mainly because this study was more thorough and investigated a comprehensive package of biological parameters. The MOE would, however, still remain < 100, meaning user safety warnings should be present to inform the user of potential adverse effects.

It also has to be taken into account that DOCP is the pivalate ester of DOC, the active moiety, and has been designed to be used as a long-acting depot injection, with effect in the dog lasting around 25 days. Therefore, there is likely to be prolonged clearance from the system of someone who has had an accidental injection. PK data from the dog demonstrates a half-life of 8 or 17 days, depending on whether the product was administered IM or SC. The T_{max} is approximately 10 days in both cases.

A calculation of the MOEs for each scenario identified has been provided, with dermal exposure and accidental self-injection being the routes of concern. The calculated MOEs were 105 and 15 respectively.

Regarding risk reduction via the use of warnings, accidental exposures via skin or eye contact can be mitigated, since systemic exposure can be eliminated by washing the area of spillage thoroughly. A NOEL of 5.4 mg/kg bw has been established for reproductive and developmental endpoints, which leads to a MOE of 37, indicating an unacceptable risk (MOE < 100) without risk mitigation measures. Potential reproductive or developmental effects need to be mitigated.

The following user safety warnings were justified based on the data available and included in the SPC and package leaflet:

- Avoid contact with the eyes and skin. In case of accidental spillage onto the skin or eyes, wash the affected area with water. If irritation occurs, seek medical advice immediately and show the package leaflet or the label to the physician.
- This product may cause pain and swelling at the injection site if accidentally self-administered.
- This product may cause adverse effects on male reproductive organs and, as a result, fertility.
- This product may cause adverse developmental effects on unborn children and neonates.
- Pregnant and breast-feeding women should avoid administration of this product.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Based on the data presented, the product does not pose an unacceptable risk to users, who are veterinarians (administering the product), when used in accordance with the SPC.

Environmental risk assessment

An environmental risk assessment has been provided, according to the VICH guidelines; the assessment stops in Phase 1, as the product is intended for use in companion animals only and it is therefore not expected that environmental exposure would be extensive.

Based on the data provided, it can be concluded that Zycortal is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Limited data have been provided on pharmacokinetics, repeat-dose toxicology, and reproductive and developmental toxicology. Data provided include two target animal safety studies, a bioequivalence study (showing equivalence between two routes of administration), a pilot study for the mouse micronucleus test and some preliminary pharmacokinetic data showing the duration and extent of absorption and elimination of the intended prolonged-release formulation in dogs. There are no data regarding metabolism or distribution of the active substance into various organs. The applicant has provided a single-dose study in rats, which showed no toxicity up to 9.6 mg/kg bw, and a screening test in rats for reproduction and development, showing no toxicity up to 5.4 mg/kg bw. The target animal safety data provided were not sufficient to derive adequate toxicological reference values for use in the user safety assessment, but the single-dose and reproduction/development screening studies conducted in rats provide reassurance that potential toxic outcomes are less likely to be realised with a one-off accidental self-injection.

Those areas that have been fully addressed include genotoxicity (DOCP can be considered as unlikely to be a genotoxin), dermal sensitisation and irritation (the product does not induce sensitisation, but it is slightly irritant to skin) and eye irritation (the product is a slight eye irritant).

A user safety assessment, in line with current guidance, has been provided and is acceptable.

The main issues relate to indications of reproductive toxicity and heart and kidney injury resulting from the use of DOCP in healthy dogs even at the recommended therapeutic dose. These adverse effects could be predicted based on the pharmacological effects of mineralocorticoids. The toxicity seen in the reproductive organs leads to a concern about developmental toxicity, which has been further investigated in the screening study performed in rats. Relevant SPC warnings have been completed accordingly. The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

An appropriate environmental risk assessment has been provided. Based on the data provided, the ERA can stop at Phase I. It can be concluded that the product is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Not applicable.

Part 4 – Efficacy

Zycortal is a 25 mg/ml suspension for subcutaneous injection for dogs, containing the active substance desoxycortone pivalate (DOCP). The proposed indication is for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease).

The proposed initial dose is 2.2 mg/kg bodyweight. Subsequent doses should be titrated on the basis of the animal's serum electrolyte concentrations and clinical signs at a proposed dosing interval of 25 days. The product is intended for long term treatment.

Pharmacodynamics

Zycortal contains 25 mg/ml of the synthetically produced mineralocorticoid desoxycortone pivalate (DOCP), and is to be used in dogs as a replacement therapy for cases of mineralocorticoid deficiency (i.e.

primary hypoadrenocorticism). DOCP is an ester of the acetate of naturally occurring desoxycortone (DOC). DOCP is converted in vivo to DOC.

Mineralocorticoids activate the mineralocorticoid receptor of target tissues which include the intestinal epithelial cells, salivary glands, sweat glands and the kidney – the major target tissue. In the kidney, mineralocorticoids primarily exert their effects on the distal convoluted tubules and to a lesser extent on the collecting ducts. They mainly cause sodium and chloride retention (accompanied with water retention due to the osmotic gradient created) and potassium excretion.

Primary hypoadrenocorticism is described in literature as the end result of an immune-mediated process causing destruction of the adrenal cortex and therefore, a deficiency of mineralocorticoid and/or glucocorticoid (primarily aldosterone and cortisol, respectively, in dogs) secretion. If left untreated, the disease has a high morbidity and mortality.

The deficiency of mineralocorticoid (as seen with primary hypoadrenocorticism) causes electrolyte imbalances that might lead to renal medullary washout, haemoconcentration, hypotension and hypovolaemic shock. Mild metabolic acidosis may also be seen. The rise in K^+ levels in association with profound hypovolaemia and hypotension may eventually lead to cardiac arrest. Therefore, treatment with exogenous mineralocorticoids and/or glucocorticoids is required to reverse the pathophysiological effects.

Zycortal is a treatment to restore electrolyte and water balance and hence control the signs of hypoadrenocorticism. Unlike some other mineralocorticoids, DOCP has limited glucocorticoid activity; thus allowing the independent dose titration of mineralocorticoid without the risk of overdosing the animal with glucocorticoid.

The pharmacodynamic properties of mineralocorticoids in the kidney (the main target tissue) are well characterised; however, activity on non-renal target tissue has not been fully characterised but is reported in literature to be involved with Na^+ and K^+ regulation in the same way as at renal epithelial cells, although the overall impact through these tissues is at a much lower magnitude.

Development of resistance

Not applicable.

Pharmacokinetics

Two preliminary single dose pharmacokinetic (PK) studies in dogs have been conducted by the applicant.

The first non-GLP study (GB009\08-001 [DOCP004]) was conducted in 4 Beagles with DOCP administered as a single dose at 10 x the recommended treatment dose (RTD) intramuscularly (IM). Serum samples were analysed for aldosterone, DOC, DOCP and corticosterone. Urine samples were analysed for DOC and DOCP. Only DOC was detected in serum and neither DOC nor DOCP were detected in urine. The applicant concluded that the study confirmed literature reports of DOCP being converted to DOC in vivo (Scott-Moncrieff, Ref 9). However, as the analytical method was not validated, the results of the study can only be considered as supportive.

The second study (GB009\09-003 [DOCP005]) was compliant with GLP-requirements, and conducted in 6 Beagles. DOCP was administered as a single dose at 5 x RTD via subcutaneous (SC) and IM routes of administration sequentially, 60 days apart, in a cross-over design. The final formulation was used and the analytical method had been validated. DOC concentration-time curves were plotted to compare the pharmacokinetic profiles between the different routes of administration. The applicant concluded from visual inspection of the graphical representation of the pharmacokinetic profiles that the two routes of

administration were similar with the exception of a longer "apparent half-life" when DOCP is administered via the SC route. The pharmacokinetic study showed that peak plasma levels of the active metabolite, DOC, were achieved between D7 to D11 and that DOC was still detectable at 25 days after administration. The prolonged-release formulation was demonstrated, with an apparent half-life of DOC of 17 days for SC administration when DOCP is administered at a dose of 11 mg/kg bw.

As this is a MUMS/limited market application, it can be accepted that not all pharmacokinetic investigations required in part 4 by standard guidance are provided. The applicant has not discussed the distribution, metabolism or elimination of DOCP, beyond the comment that it is converted to the active metabolite DOC (21-hyodroxyprogesterone). No dose linearity studies and no repeat dose studies have been conducted or presented for DOCP. However, although some initial accumulation might be expected to occur with the proposed dose interval, the lack of repeat dose studies is considered acceptable in light of the fact that the titration of subsequent doses and dosing intervals is based on the individual animal's serum electrolyte concentrations, and taking into account the MUMS/limited market designation.

Dose determination/justification

No dose determination studies have been conducted with the candidate formulation. The proposed justification of dose is based on the published literature from several US clinical studies (Lynn et al*,* 1993, Melian and Peterson, 1996, Percorten-V FOI Summary) or retrospective case series (Kintzer and Peterson, 1997, Bates et al*,* 2013), using an FDA-licensed Canine Addison's Disease product containing desoxycortone pivalate (Percorten-V). None of the studies included a control group.

The studies all report an initial dose of 2.2 mg/kg of DOCP administered intramuscularly (IM), as opposed to the subcutaneous (SC) route for Zycortal. Electrolyte concentrations (Na^+, K^+ and Na^+ K^+ ratio) were measured approximately 10 days after dosing and again, prior to administration of the next dose (intended to be 25 days after the previous dose). Subsequent doses and dosing intervals are titrated on the basis of the individual animal's serum electrolyte concentrations. A guidance table is presented in the proposed SPC for Zycortal to assist the veterinary surgeon in doing this.

Based on the comparability of the pharmacokinetic profiles for IM and SC administration demonstrated in study GB009\09-003, the confirmatory evidence from a field trial and the consideration that this is a MUMS/limited market application, the dose justification is considered satisfactory.

Target animal tolerance

In support of target animal safety, the applicant provided the results of a pivotal target animal safety (TAS) study, as well as supportive, published studies using another DOCP product authorised in the USA, and results from the field trials.

Pivotal TAS study (DP300-TAS-01)

The applicant conducted one pivotal GLP compliant target animal safety (TAS) study (DP300-TAS-01) with the final formulation. DOCP was administered SC to 32 healthy Beagles (5-6 months old, 7–9 kg bw at the start of the study) at 0, 2.2 mg/kg bw (1x the recommended treatment dose; RTD), 6.6 mg/kg bw (3x RTD) or 11 mg/kg bw (5x RTD) every 21 days for six months (8 animals per group). This is consistent with VICH guidance. General health observations were conducted twice daily and bodyweights were checked on Study Days -13, -1, 1, 20, 41, 62, 83, 85, 104, 125, 146, 167 and 180. On Study Days -13, -7, 1, 85 and 180, clinical examinations were performed (except Day -7) venous blood samples taken and urine samples were collected.

There were no serious, treatment-related adverse events in any group. Although statistically significant changes in serum biochemistry, electrolytes and haematology were reported in treated groups compared to the control group, values remained within normal laboratory reference limits except on a few occasions for individual animals. There were increases in serum globulin and sodium concentrations and decreases in urea and potassium in treated animals compared to the control group. Haematology showed statistically increased neutrophils and decreased lymphocyte counts. A statistically and clinically significant, dose-dependent decrease in urine specific gravity was also reported. Statistically significant increases in heart and kidney weights, and a decrease in the weight of ovaries, were also observed in the treated groups.

Irregular white plaques were noted at the injection sites of all treated groups and correlated with microscopic granulomatous inflammation in the subcutaneous tissue (although only considered statistically significant in the 3x and 5x RTD groups when compared to the control group). This was dose-dependent and considered to be related to administration of the test product; however, no intervention was required. It is likely that this is related to the crystalline nature of the formulation to support a depot release of DOCP. No injection site reactions were reported in the field trial.

Other than injection site reactions at overdose, the observations in this study can be explained largely by the pharmacological/physiological effects that would be expected from a mineralocorticoid, and it is noted that even at 5x RTD in healthy dogs, the product was clinically relatively well tolerated.

Published data

The findings of the target animal safety study (DP300-TAS-01) are consistent with the studies reported in literature (Chow et al, 1993, Ref 21; FDA FOI Percorten-V Summary; Lynn and Feldman, 1991) where a DOCP preparation authorised in the USA (Percorten-V) was administered IM.

In the "repeat-dose" study by Chow et al., 1993 (also described in part 3 of this report), 24 Beagles were treated with either 0x, 1x, 3x or 5x RTD on three consecutive days, every month for six months (equivalent to a cumulative monthly dose of 0x, 3x, 9x, of 15x RTD respectively). As the study is reported in literature, limited clinical parameters are available. There was a statistically significant decrease in the weight of testes and epididymides in treated male dogs compared to the control group. Some electrolyte changes are reported (increased Na^+, decreased K^+) and otherwise the findings support the authors' conclusion that DOCP is well tolerated when administered at the RTD.

Very common adverse events following the treatment with Zycortal in the field study (DP300-EEF-01, see below) included polydipsia (48.7%), polyuria (46%), vomiting (42.5%), polyphagia (27.4%), diarrhoea (25.7%), inappropriate urination (24.8%), lethargy (21.2%), and loose stools (20.4%). All events were considered non-serious.

Overall, the data support a conclusion that Zycortal is expected to be well tolerated when administered at the RTD in accordance with the SPC, especially as adverse effects are related mostly to the physiological effects of mineralocorticoids and would represent a normalisation of physiological function when the product is used as replacement therapy for dogs with hypoadrenocorticism. The SPC accurately reflects the most common side effects seen in the TAS studies, scientific literature and field trial.

Field trials

One GCP-compliant multi-centre efficacy field trial (DP300-EEF-01) was conducted to investigate the effectiveness of Zycortal for use as replacement therapy for dogs diagnosed with primary adrenocortical insufficiency (hypoadrenocorticism). The study enrolled 152 animals across 13 sites in the USA and two

sites in France. Of these, 74 dogs were male (9 entire, 65 castrated), and 78 were female (10 entire, 68 spayed). Mean age was 4.7 ± 2.7 years (range 0.5–12.4 years) and the most common breed in both groups was mixed breed (43 dogs [38.1%] in the test product group; 11 dogs [28.2%] in the control group). Other common breeds included Poodle (9 dogs [8.0%] in the test product group, 1 dog [2.6%] in the control group), Labrador Retriever (6 dogs [5.3%] in the test product group, 1 dog [2.6%] in the control group), West Highland White Terrier (5 dogs [4.4%] in the test product group, 2 dogs [5.1%] in the control group) and Great Dane (3 dogs [2.7%] in the test product group, 2 [5.1%] dog in the control group). Other breeds were represented by four or fewer dogs in each group.

Animals were randomised into treatment groups at a ratio of 3:1 and treated with the test candidate formulation (n=113) or a positive control product (Percorten-V, Novartis Animal Health) (n=39), respectively. Percorten-V is a 25 mg DOCP/ml suspension for injection which is authorised in the US, Canada and Australia but not in the EU. The applicant reports that the excipients in Zycortal differ slightly from Percorten-V, the former containing the surfactant polysorbate-60 rather than polysorbate-80, and the preservative chlorocresol rather than thiomersal. At the time of assessment, there are no EU-authorised veterinary medicinal products for mineralocorticoid supplementation in cases of canine primary hypoadrenocorticism. Fludrocortisone is commonly used in the EU under the Cascade as maintenance mineralocorticoid therapy but has more glucocorticoid activity than DOCP and is therefore not a suitable positive control. Considering that the disease can present as acute hypoadrenal crisis, for ethical reasons it is acceptable that there was no placebo control group.

For the analysis of study data for the purposes of authorisation in the EU, the applicant established the proportion of all the cases treated with Zycortal that were considered to be treatment successes at Day 90 and 180 ± 14, relative to their baseline parameters (clinical signs, Na^+ and K^+ values and ratios). As hypoadrenocorticism can present as an episodic disease in addition to a progressive one, the analysis using animals as a "self-control" may not be considered to be fully robust, although it would be expected that disease would have progressed in most animals by Day 90. For the purpose of the authorisation of Zycortal in the US, the applicant elected to demonstrate non-inferiority of the candidate formulation to Percorten-V. The FDA Freedom of Information (FOI) report documenting the US approval for Percorten-V is provided. The effectiveness of Percorten V was originally evaluated on the basis of clinical signs, renal parameters and electrolytes, with animals serving as their own controls. The lack of evidence of this product's effectiveness derived from a placebo-controlled study might raise concerns in regards to the internal validity of the analysis comparing Zycortal to Percorten-V. Despite all these various concerns, the limited options for the control group outlined above are acknowledged. Therefore, on these grounds, the comparison to baseline analysis provided for Zycortal is accepted with the supportive evidence from the non-inferiority to Percorten-V analysis.

Zycortal was administered by SC injection at a starting dose of 2.2 mg DOCP/kg bodyweight. Subsequent doses and treatment intervals were determined according to individual patient need and based on the monitoring of Na^+/K^+ ratio in accordance with the proposed SPC for a follow up period of 6 months. Percorten-V was administered by IM injection, consistent with the US authorisation. In addition, oral glucocorticoids (prednisone/prednisolone) were administered at an initial dose rate of 0.2–0.4 mg/kg bodyweight to all dogs. The glucocorticoid dose was then adjusted during the study according to patient need, with final dose in the range 0.011 to 0.513 mg/kg bw in the test group.

Clinical examinations and Na^+/K^+ ratio were evaluated at D0 (treatment), and thereafter approximately on D10, 25, 60, 90, 120, 150 & 180. Haematology and biochemistry were also monitored before treatment and on D25, 60 & 90. "Clinical improvement" was assessed on the basis of a physical examination, the presence of 7 key clinical signs, owner observations and clinical pathology.

In this trial, a dog was considered a treatment success if the clinical signs and observations had improved

from baseline (i.e. at time of diagnosis) ("clinical improvement") or the dog had remained clinically normal, and the in-house serum Na^+ and K^+ concentrations were within normal limits or the Na^+/K^+ ratio was between 27 and 32.

Alternatively, a dog was considered a treatment failure if the clinical signs and symptoms had not improved from baseline or the dog had not remained clinically normal or the in-house serum Na^+ and K^+ concentrations or ratio were not within normal limits or the dog did not complete the study through Visit 6 due to an adverse event related to Zycortal or the control product.

The primary efficacy outcome was treatment success at D90 ± 14 days and the secondary outcome was success at D180 ± 14 days. As indicated above, the applicant evaluated the effectiveness of Zycortal by comparing the D90 findings to the baseline (D 0) for this group (per cent treatment success). In addition, the non-inferiority (margin 15%) of Zycortal to the control product, Percorten-V, was also analysed.

It is recognised that in practice, resolution of clinical signs is the key factor for determining treatment success or failure. The use of a binary methodology for scoring the 7 key individual clinical signs could be criticised for reducing discriminatory power; however, additionally the decision on clinical improvement was based on an extensive and well recorded database also including physical examination, clinical pathology and owner observations. Treatment success/failure was also based on the objective endpoint of serum Na^+/K^+ ratio or levels being within the reference ranges. This is a sensitive and specific diagnostic test (89% and 97%, respectively, Adler 2007) and is considered an acceptable outcome measure for the purposes of the trial.

Results

The mean final dosage was 1.94 ± 0.27 mg DOCP/kg bw in the Zycortal group and 1.96 ± 0.27 mg DOCP/kg bw in the Percorten-V group. The mean final dose interval was 38.7 days (range 20–99 days) for Zycortal and 42.4 days (range 23–182 days) for Percorten-V.

Initially a Per-Protocol (PP) analysis was performed; however, the applicant has also conducted an Intention-To-Treat (ITT) analysis (in accordance with the current guideline on statistical principles for clinical trials for veterinary medicinal products EMA/CVMP/EWP/81976/2010). For this analysis, missing data mostly appeared to relate to dogs which had longer inter-dosing intervals and therefore missed the window for the D90 data collection. However, these dogs did remain in the trial beyond D90, and probably for the full duration. The missing data have been handled using "last observation carried forward" approach.

The treatment success and evaluation of non-inferiority for the ITT and PP populations at 90 and 180 days are summarised below.

	Day 90		**Day 180**	
	Zycortal	**Percorten-V**	**Zycortal**	**Percorten-V**
Treatment success - compared to baseline*	*86.24%* *(n=101)* 84.55% (n=109)	*85.13%* *(n=34)* 84.06% (n=38)	*88.32%* *(n=79)* 86.54% (n=109)	*86.90%* *(n=26)* 84.25% (n=38)
Baseline comparison*: Lower bound of 95% CI	*77.84%* 76.21%	N/A	*77.95%* 78.32%	N/A

Non-inferiority*: Upper bound of 95% CI (CP-IVP)	*13.56%* 13.78%	*18.31%* 13.77%

* *PP population (italics)*; ITT population (normal font)

There were 3 serious adverse events in the Zycortal group during the study, but the relationship to treatment was considered to be unlikely or unknown. The most common non-serious adverse events in the Zycortal group included: polydipsia (48.7%), polyuria (46.0%), vomiting (42.5%), polyphagia (27.4%), diarrhoea (25.7%), inappropriate urination (24.8%), lethargy (21.2%), and loose stools (20.4%). Of these, polyuria (15%), polydipsia (13.3%) and inappropriate urination (8%) were considered to be probably or possibly related to the test treatment. These signs are likely to be related to the pharmacological action of the active substance.

In conclusion, 92 of 109 (84.4%, lower 95% CI 78.3%) dogs in the ITT population diagnosed with hypoadrenocorticism showed treatment success (clinical improvement and normalisation of Na^+ and K^+ levels [or Na^+ K^+ ratio]) when compared to baseline after 90 days treatment with Zycortal and prednisone/prednisolone. After 180 days, 94 of 109 (86.24%) dogs in the ITT population were classed as treatment success. In addition, the effectiveness of Zycortal was shown to be non-inferior to that of Percorten-V, authorised in the US for treatment of the same condition. The assessment of the one GCP compliant multi-centre efficacy field trial is supportive of the product's effectiveness.

Other studies

None.

Overall conclusion on efficacy

Desoxycortone pivalate is rapidly metabolised to desoxycortone, a naturally occurring mineralocorticoid hormone. The pharmacodynamic effects of mineralocorticoids in the kidney (the main target tissue) are well characterised, including retention of sodium and chloride in the renal tubule and excretion of potassium. Thus, DOC restores the water and electrolyte imbalance that occurs in primary hypoadrenocorticism. A pharmacokinetics study in dogs conducted with the final formulation, but at 5x RTD, confirmed the prolonged-release nature of the formulation in the target species. Peak plasma levels of the active metabolite, DOC, were achieved between D7 to D11 and DOC was still detectable 25 days after administration.

A combination of retrospective and prospective literature studies on the management of canine primary hypoadrenocorticism have been presented to justify the dose. The recommended starting dose of the proposed formulation is 2.2 mg DOCP /kg bw with subsequent treatment doses being titrated according to patient need (subsequent dose range between 2.0 and 2.4 mg DOCP/kg bodyweight and decided on the basis of serum Na^+ and K^+ values and ratio). This posology is largely consistent with what has been reported in the literature presented.

Despite the fact that literature refers to administration of the dose predominantly by the IM route, the comparative bioavailability study (GB009\09-003 [DOCP005]) in the pre-clinical sections suggests that it is reasonable to extrapolate these results to the SC route. The initial dose of 2.2 mg/kg bodyweight is further supported by the demonstration of this treatment dose being well tolerated in the target animal safety study (DP300-TAS-01). No further data are required to justify the dose.

A classical GLP target animal safety study was provided. Other than injection site reactions at overdose, the observations can largely be explained from the pharmacological/physiological action of a mineralocorticoid: effects on electrolytes, urea and urine specific gravity.

A multi-centre efficacy field trial (DP300-EEF-01) was conducted with 152 animals. The dogs were randomised into treatment groups in a ratio of 3:1 and treated with the test candidate formulation or a positive control DOCP product (Percorten-V), respectively. Ninety-two out of 109 (84.4%, lower 95% CI 76.21%) dogs in the ITT population diagnosed with hypoadrenocorticism showed treatment success (clinical improvement and normalisation of Na^+ and K^+ levels (or Na^+/K^+ ratio)) when compared to baseline after 90 days treatment with Zycortal and prednisone/prednisolone. After 180 days, 94 of 109 (86.2%) dogs were classed as treatment success.

In addition, the effectiveness of Zycortal was shown to be non-inferior to that of Percorten-V, authorised in the US for treatment of the same condition. The assessment of the GCP compliant multi-centre efficacy field trial is supportive of product effectiveness. Adverse events considered to be probably or possibly related to the test treatment included polyuria (15%), polydipsia (13.3%) and inappropriate urination (8%). These signs are likely to be related to the pharmacological action of the active substance.

Part 5 – Benefit-risk assessment

Introduction

Zycortal is a 25 mg/ml prolonged-release suspension for injection containing the active substance desoxycortone pivalate (DOCP) and is presented in multi-dose vials containing 4 ml.

Desoxycortone pivalate is a corticosteroid with primarily mineralocorticoid activity which acts as a precursor to aldosterone, the actions of which result mainly in sodium and chloride retention (accompanied with water retention due to the osmotic gradient created) and potassium excretion.

The product is intended for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease). The recommended starting dose is 2.2 mg/kg bodyweight; administered via subcutaneous injection, at a proposed dosing interval of 25 days. Subsequent doses and dose intervals should be titrated on the basis of the animal's serum electrolyte concentrations.

The product has been classified as MUMS/limited market and therefore reduced data requirements apply and these have been considered in the assessment.

This is a full application submitted in accordance with Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The direct therapeutic benefit of Zycortal is its efficacy as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease), by restoring electrolyte and water balance and hence the control of the signs of hypoadrenocorticism in dogs.

After SC administration, peak plasma levels were achieved in 7 to 11 days and levels were still detected at 25 days after administration. This is relevant for treatment of a chronic condition.

Taking into consideration the MUMS/limited market nature of the application, the dosing regimen is considered to be adequately supported.

Clinical efficacy was demonstrated in a multi-centre efficacy field trial conducted in the EU and USA. Animals were randomised into treatment groups in a ratio of 3:1 and treated either with Zycortal or a positive control (Percorten-V), respectively. Treatment success was based on evaluation of clinical signs and normalisation of electrolytes. 84.4% of dogs diagnosed with hypoadrenocorticism showed treatment success (clinical improvement and normalisation of Na^+ and K^+ levels (or Na^+/K^+ ratio)) when compared to baseline after 90 days treatment with Zycortal and prednisone/prednisolone. After 180 days, 94 of 109 (86.2%) dogs were classed as treatment success, demonstrating that the product is efficacious as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease).

Additional benefits

If left untreated, canine primary hypoadrenocorticism has a high morbidity and mortality. Zycortal would provide the first authorised veterinary medicinal product in the EU for the treatment of canine primary hypoadrenocorticism.

At present, treatment involves the daily administration of synthetic mineralocorticoid tablets authorised for human use. The prolonged release properties for Zycortal result in a treatment interval of 25 days, which is expected to increase owner compliance when compared to the daily administration of tablets.

Risk assessment

Main potential risks

Quality:

The formulation and manufacture of the finished product is well described and specifications set will ensure that product of consistent quality will be produced.

Target animal safety:

Treatment at the recommended dose of 2.2 mg/kg bw is generally well tolerated in healthy dogs both via IM and SC administration. Adverse effects are consistent with the pharmacological action of mineralocorticoids.

In a field trial, common adverse events included polydipsia (48.7%), polyuria (46.0%), vomiting (42.5%), polyphagia (27.4%), diarrhoea (25.7%), inappropriate urination (24.8%), lethargy (21.2%), and loose stools (20.4%).

User safety:

Based on the available information a risk associated with use of the product by pregnant women, related to developmental and/or reproductive toxicity cannot be ruled out. Data provided also indicate potential toxicity in the kidneys, heart, and in male reproductive organs. The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose a risk to the environment when used in accordance with 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 the environment and to provide advice on how to prevent or reduce these risks.

User safety risks have been identified, mainly concerning the risks associated with exposure of reproductive organs. These risks have been addressed by the safety warnings in the SPC.

Evaluation of the benefit-risk balance

The benefit of Zycortal prolonged-release suspension for injection is its efficacy as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease).

The formulation and manufacture of the product is well described and the proposed specifications would ensure that a product of consistent quality will be produced.

It is well tolerated by the target animals.

The product represents an acceptable risk for the user and the environment when used as recommended and appropriate warnings have been included in the SPC.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on the benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

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 Zycortal 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.