EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Procox (as published in May 2011). For information on changes after this date please refer to module 8.

1. Summary of the dossier

Procox, an oral suspension, contains the active substances emodepside and toltrazuril and is presented in bottles of 7.5 ml or 20 ml. The target species is dogs (puppies). It is indicated for dogs suffering from, or at risk from, mixed parasitic infections caused by roundworms and coccidia of certain specified species. The applicant for this veterinary medicinal product is Bayer Animal Health GmbH, Germany. The product was eligible for the Centralised procedure under Article 3 of Regulation (EC) No 726/2004.

The two active substances in Procox are emodepside (0.9 mg/ml) and toltrazuril (18 mg/ml). Emodepside is a depsipeptide antiparasiticide which acts at the neuromuscular junction by stimulating presynaptic receptors belonging to the secretin receptor family, resulting in paralysis and death of the parasites. Toltrazuril is an anticoccidial which acts against all intracellular development stages of the coccidia, resulting in their death.

The benefits of Procox are its efficacy against the replication of coccidia and the shedding of oocysts at all stages of coccidial infection. The most common side effects are slight and transient digestive tract disorders, such as vomiting or loose stools.

The approved indication is:

> For dogs, when mixed parasitic infections caused by roundworms and coccidia of the following species are suspected or demonstrated:
>
> Roundworms (Nematodes):
> - *Toxocara canis* (mature adult, immature adult, L4)
> - *Uncinaria stenocephala* (mature adult)
> - *Ancylostoma caninum* (mature adult)
>
> Coccidia:
> - *Isospora ohioensis* complex
> - *Isospora canis*

Procox is effective against the replication of *Isospora* and also against the shedding of oocysts. Although treatment will reduce the spread of infection, it will not be effective against the clinical signs of infection in already infected animals.

The GMP status of the dosage form manufacturing, assembly and release sites is satisfactory.

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The pharmacovigilance system in place complies with the requirements in the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products in Volume 9 of the Rules governing medicinal products in the EU.

2. Quality assessment

Composition

Procox is a non-aqueous (oily) oral suspension containing emodepside and toltrazuril (both active substances), sunflower oil (vehicle), glycerol dibehenate (thickener), butylhydroxytoluene (anti-oxidant) and sorbic acid (preservative).

Container

Procox is packaged in two different sized brown glass bottles containing 7.5 ml or 20 ml suspension, with a plastic syringe adapter (low density polyethylene (LDPE)) and a screw cap (polypropylene (PP)). The container/closure is child-resistant, even after first opening, and confirmation of compliance with ISO 8317:2003 has been provided. The outer packaging is cardboard cartons.

Syringes are not supplied with the product, which is intended to be administered with commercially available syringes. The SPC (and package leaflet) include clear instructions to this effect.

All the materials in contact with the product comply with Directive 2002/72/EC and the relevant Ph. Eur. requirements. During the stability studies, possible interactions between the product and the packaging were investigated, but no evidence of any leaching, adsorption or absorption was observed.

Development pharmaceutics

A liquid formulation for oral use was developed since to enable accurate and precise dosing to puppies, as well as convenience for the animal owner. The choice of the formulation is based on the solubility and stability of the two active substances in various solvents and the toleration by the target species of these formulations.

The particle size of the toltrazuril was optimised to ensure a stable and homogeneous suspension, and data demonstrate the particle size reduction can be done in a reproducible manner. Emodepside is partly dissolved but mostly in suspension in the sunflower oil.

Glyceryl dibehenate was selected for its ability to minimize sedimentation of the suspension. The chosen contents of the antioxidant, butylhydroxytoluene, and the preservative, sorbic acid, have been extensively evaluated and their inclusion fully justified.

Method of manufacture

The manufacture of the suspension can be divided into three major steps. Firstly, an intermediate toltrazuril suspension concentrate is manufactured by mixing and milling. In the second step all the excipients are mixed and a solution is formed (using heat and stirring). In the third step the suspension concentrate and the second active substance, emodepside, are added to the excipient solution. The resultant suspension is then cooled prior to filling into bottles, with nitrogen filling of the headspaces prior to capping. Appropriate in-process controls are proposed.

The process is straightforward and considered as a standard process. Validation of pilot-scale batches indicates that the manufacturing process yields a robust reproducible product. Full production scale process validation will be performed prior to launch.

Control of starting materials

Active substance (toltrazuril)

Toltrazuril is an established active substance but is not described in any pharmacopoeia. The synthesis has been described in sufficient detail. Adequate information on the synthesis and control of the starting materials has been provided. The process is evaluated based on representative batches. In the absence of a pharmacopoeial monograph, emodepside is controlled by a comprehensive in-house specification. The control tests and specifications for toltrazuril are suitable to ensure a product of consistent quality is produced. The proposed limits for impurities are justified according to the VICH guideline on impurities in drug substances. Appropriate validation and batch data have been provided.

Toltrazuril is considered to be a stable substance under VICH conditions. Formal VICH and stress stability studies have been performed. A re-test period of 24 months in the specified packaging, with no special storage conditions, is justified by long term data of up to 5 years and 6 months accelerated stability results.

Active substance (emodepside)

Emodepside is an established active substance but is not described in any pharmacopoeia. It is a semi-synthetic compound, the starting material for the chemical synthesis of which is produced by fermentation of the fungus *Mycelia sterilia.* All steps in the manufacture of emodepside are well described. The synthesis has been described in sufficient detail. Adequate information on the synthesis and control of the starting materials has been provided and the specifications and methods for the reagents, solvents and intermediates are appropriate. Routine in-process controls are included at each stage of the process and are considered appropriate. The process is evaluated based on representative batches. In the absence of a pharmacopoeial monograph, emodepside is controlled by a comprehensive in-house specification. Methods are described and limits justified where appropriate. Appropriate validation and batch data have been provided.

Based on the long term and accelerated stability data provided, a retest period of 36 months in the specified packaging is justified.

Excipients

The excipients, butylhydroxytoluene, sorbic acid, glycerol dibehenate and refined sunflower oil are each controlled according to the requirements of the respective Ph. Eur. monograph, and their compliance has been demonstrated. Ph. Eur. quality nitrogen is used as a headspace gas during manufacture. Satisfactory certificates of analysis are provided for each of the excipients.

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

No ingredients are of bovine, ovine or caprine origin, nor are any animal ingredients used during the processing of the excipients or the final medicinal product. For this reason there is no risk of transmission of spongiform encephalopathy (according to the Ph. Eur. general chapter 5.2.8. "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products") from this product.

Control tests

Control tests on intermediates

The intermediate, toltrazuril suspension concentrate, is controlled when manufactured by appropriate methods and limits. Satisfactory stability data on this intermediate have been provided, and the start of shelf-life is set in accordance with the relevant guideline.

Control tests on the finished product

The finished product is controlled according to a satisfactory and justified specification in line with relevant VICH Guidelines and suitable for this type of dosage form (appearance, identity, suspendability, viscosity, particle size, assay, degradation products, microbial quality, and extractable volume). The absence of a test and limits for dissolution has been fully justified. The methods have been described in sufficient detail. The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product and justified. The results from three production batches confirm compliance to the proposed specifications.

Stability

The results of the submitted stability data on three batches (24 months storage at normal storage conditions; 12 months at intermediate storage conditions; and 6 months at accelerated storage conditions) justify the proposed shelf life of 24 months without any specific storage condition. The stability study is on-going.

An in-use stability study was performed and the results justify the product is stable over the in-use shelf-life of 10 weeks.

Overall conclusions on quality

The dossier provides appropriately detailed descriptions of both of the active substances and the final product formulation, and demonstrates that production of the active substances and the product leads to a consistent quality. The analytical methods are well described, and data of their validation confirm their suitability. Stability studies have been performed according to the relevant VICH guidelines. The primary stability studies on the finished product are on-going. The stability studies on the active substance justify re-test periods for toltrazuril and emodepside of 24 months and 36 months respectively. For the finished product, a shelf-life of 2 years with no restrictions on storage conditions and an in-use shelf-life of 10 weeks have been justified.

Overall the documentation on quality relating to both of the active substances as well as the final product is satisfactory and provides reassurance that a product of consistent quality will be produced.

3. Safety assessment

Pharmacodynamics

The mode of action for emodepside and toltrazuril is described in Part 4.

Emodepside may have an effect on vasodilation in dogs when administered by the intraduodenal route at a dose of 1.5 mg/kg bw (bodyweight). Effects on glucose metabolism were seen in rats after oral administration of 3 mg/kg bw. In addition it is noted that when administered orally at high doses,

emodepside elicited abnormal behaviour in rats (characterised by decreased locomotor activity as well as posture and gait abnormalities): these effects were seen at doses of 30 and 100 mg/kg bw, with a NOAEL of 10 mg/kg bw. Compared to ivermectin, emodepside is more effectively effluxed in MDR-1 cells, and this active transport is not saturable in the concentration range tested. These data suggest that emodepside will not be able to cross membranes such as the blood-brain barrier. However, given that there is the potential for interaction with other P-glycoprotein dependent substrates, an appropriate warning statement is included in section 4.8 of the SPC.

Toltrazuril has no specific secondary/safety pharmacology effects. It induces a non specific inhibition of the bronchial smooth muscle contraction at 10 µg/ml. A moderate increase in blood pressure and in peripheral resistance in dogs, and a slight decrease in the sodium elimination was seen at 100 mg/kg bw. A NOAEL of 10 mg/kg bw was established.

Ponazuril (toltrazuril sulphone) is the major metabolite of toltrazuril. It was shown to have a slight vasorelaxant effect in the anesthetised dog, and induced an increased ulceration in rats at 30 mg/kg bw and above. Additionally, the triglyceride level decreased slightly when administered at 100 mg/kg bw to fasted rats. Overall though, ponazuril showed no specific pharmacodynamic activities which would affect those of the parent substance, toltrazuril.

No pharmacodynamic studies have been performed with the combination.

Pharmacokinetics

Emodepside

The pharmacokinetics of emodepside has been studied in rats and dogs. An absorption/distribution/ metabolism/excretion (ADME) study in rats showed that there is no sex or dose-related differences in the rate and route of excretion after single or repeated administration of emodepside. The absorption is dependent on the vehicle. The faecal route of excretion predominates. Emodepside has an elimination half-life in rats of 39-51 hours and a bioavailability of 47-54% after oral administration. The highest residues are found in fat, which may act as a depot. Unchanged emodepside is the major excretion product, accounting for 45-56% of the dose. Major metabolites were identified as three ring-hydroxylated products, while four other metabolites were shown to be hydrolysis products of emodepside.

In vitro studies in rats and dogs showed that the plasma protein binding activity is high (≥99%) and that emodepside is also taken up into erythrocytes.

In dogs, plasma concentrations were measured in the scope of the toxicology studies.

Toltrazuril

After a single oral administration of 20 mg/kg bw of ^{14}C-toltrazuril to rats, the maximum plasma radioactivity levels, in the magnitude of 25 to 36 µg equivalents toltrazuril/ml, were reached 8 and 24 hours after administration in males and females, respectively. The elimination half-lives of radioactivity differed significantly according to sex: 75 hours in females; 23 hours in males.

83 to 90% of the radioactivity administered to rats was eliminated within 168 hours in the excreta, faecal excretion accounting for 84% to 96% of the recovered radioactivity. Only 2 to 6% was excreted via the urine.

Unchanged toltrazuril was the main radioactive component detected in the faeces, accounting for 64.4 to 92.8% of the faecal radioactivity. Four metabolites were identified in faeces. One major metabolite, toltrazuril-sulfone, represented 4.6 to 16.0% of the faecal radioactivity. Two other metabolites, the

toltrazuril-sulfoxide and the sulfide of the hydroxymethyl analogue of toltrazuril accounted for less than 1%. The sulfone of the hydroxymethyl analogue of toltrazuril was only seen in faeces from males.

The main pathways of biotransformation proceeded via stepwise sulfoxidation and hydroxylation of the methyl group in the phenylene moiety.

There is indication for an accumulation of toltrazuril and its main metabolites in the serum of female rats receiving repeated doses of 30 mg/kg bw toltrazuril.

In female dogs, plasma concentrations were measured within the scope of a 7 day oral toxicity study.

Emodepside and toltrazuril in combination

Emodepside and toltrazuril were administered in combination to rats for 4 weeks. The systemic availability of emodepside appeared to be influenced, leading to a lower exposure. The vehicle used may have influenced the absorption.

(Pharmacokinetic studies on the final formulation can be found in Part 4.)

Toxicology

Single dose toxicity

Single dose toxicity studies have been performed in rats and mice. Not all studies were GLP-compliant.

Emodepside appears to be of low acute toxicity when administered by a variety of routes. Clinical signs include ataxia, piloerection, decreased motility and dyspnoea.

Toltrazuril also appears to be of low acute toxicity. Clinical signs include reduced motility, diarrhoea, polyuria and ruffled fur. Its main metabolite (ponazuril) is less toxic than the parent compound.

Acute toxicity studies on the combination can be found under the heading "Studies on formulation" below.

Repeat dose toxicity

Emodepside

All studies were GLP compliant and well conducted. The adverse effects of treatment on clinical signs, body weight gain, haematology/biochemistry and necropsy observations were remarkably consistent from study to study. The studies presented have accurately and consistently identified the repeat dose toxicity profile of this compound.

Repeated dose toxicity studies after oral administration of emodepside were conducted in rats and mice for up to 17 weeks. The effects shown in these studies include reduction in weight gain; effects on neurological function, behaviour and respiration; reduction in the absolute weight of the testes; increase in the relative weight of the brain in male rats; ataxia; increased motility; piloerection; increase in glucagon-secreting cells, with a trend towards significant hyperglycaemia; polydipsia and polyphagia. The liver (increased enzyme activity and reduced protein synthesis), adrenal glands, pancreas and reproductive system were the principal target organs for toxicity.

Studies in dogs and mice however, showed no significant or consistent hyperglycaemia, nor altered metabolism of fat and proteins or increase in food consumption. It is noteworthy that many histopathological changes did not reverse during the 4 week recovery period.

From the studies in rats, the NOEL was 0.73-1.11 (subchronic) and 4.4-4.6 (subacute) mg/kg bw. In mice, the NOEL was 10.5-16.8 mg/kg bw.

In a subacute oral toxicity study, dogs were given emodepside doses of 0, 5, 10, 20 mg/kg bw orally by gavage daily for 4 weeks, with a 4 week recovery period. The main findings were a decrease in food intake in females. Body weight gains were slightly reduced. However, body weight gains in the high dose animals were comparable to that of the controls during the 4 week recovery period. There were no mortalities. Increased episodes of vomiting and tremor/ataxia were noted in males at dose rates ≥10 mg/kg bw. Females exhibited tremor/ataxia at ≥10 mg/kg bw, with staggering, incoordination and reduced overall health status at 20 mg/kg bw. The NOAEL was 5 mg/kg bw. The CVMP noted that there was a low incidence of tremor/ataxia in low dose males (5 mg/kg bw) and it was proposed not to establish a NOEL from this study.

In another subacute oral toxicity study, dogs were given emodepside twice a day (2.5, 5.0, 7.5 mg/kg bw) for two weeks. A NOAEL of 2 daily doses of 5 mg/kg bw (2 x 5 mg/kg bw) was retained, based on changes in liver enzymes.

A repeated dose toxicity study of emodepside after dermal application was performed in rats, with an observation period of 4 weeks. There was no significant increase in erythema or in skin fold thickness. However, histopathology revealed mild acanthosis and inflammatory cell infiltration. Systemically, there were discoloured faeces and increased production of both urine and faeces at the highest dose level. A NOEL of 100 mg/kg bw can be retained for the study.

Toltrazuril

In a three month oral toxicity study in rats, toltrazuril was administered at dose levels of 0, 15, 60 and 240 mg/kg feed (approximately 0, 1.1, 4.2 and 16.6 mg/kg bw/day in males and 0, 1.2, 4.7 and 17.4 mg/kg bw/day in females). At the highest dose, the weight gain and the daily feed intake were significantly decreased. Slight effects on haematological parameters and disturbances of liver function were also observed. At 15 mg/kg feed, variations in some parameters, although statistically significant were not considered relevant because they were not dose-related. The dose of 15 mg/kg feed (1 mg/kg bw/day) can be retained as the NOEL for this study.

A second 3 month oral toxicity study was conducted in dogs administered toltrazuril at doses of 0, 1.5, 4.5 and 13.5 mg/kg bw/day. The highest dose induced a significant increase in weight of the heart without any histological changes or circulatory disturbance. The mean weights of the testes and the prostate were decreased. The NOEL retained was 1.5 mg/kg bw/day.

Ponazuril

Repeat dose toxicity studies with ponazuril (the major metabolite of toltrazuril) were performed for a period of 13 weeks by administration of ponazuril in the diet of both rats and dogs. The effects seen were similar to those for the parent substance toltrazuril. Reductions in feed intake and body weight development, and effects on red blood cells were seen in rats, and effects on feed intake/bw development in dogs. Ponazuril appears to be less toxic than toltrazuril with higher NOELs. The NOEL in rats were 150 ppm, corresponding to 11.2 mg/kg bw in males and 14.7 mg/kg bw in females.

Emodepside and toltrazuril in combination

Two subacute oral studies were performed in rats.

In one study rats were given 0, 1, 3 or 10 mg toltrazuril/kg bw and 0, 0.05, 0.15 or 0.5 mg emodepside/kg bw for 30 days. The administration was tolerated without signs of overt toxicity. In another study rats were given 0 or 20 mg toltrazuril/kg bw and 0 or 1 mg emodepside/kg bw for 30 days. The effects seen were in line with effects seen in the studies with the substances alone, with increased water intake and changes in haematological parameters. A new observation was changes in the grip strength. However, that parameter had not been tested in most previous studies. Taking both

studies into consideration, a NOEL of 10 mg toltrazuril/kg bw and 0.5 mg emodepside/kg bw was established.

Tolerance in the target species

No tolerance studies have been performed with emodepside or toltrazuril in dogs. Target animal tolerance work with the finished product is presented in Part 4. Information on the toxicology, irritation and sensitization potential of a combination of the two drug substances in final formulation is presented in this section.

Reproductive toxicity

Emodepside

A pilot one-generation study was performed in rats with doses of 0, 20, 50 or 300 ppm in the diet for 4 weeks prior to and during mating, during the resultant pregnancy and up to weaning of the F1 offspring. The mean litter size at birth and the pup weight gain were decreased at 300 ppm. Some pups exhibited uncoordinated gait and/or protruding eyeballs. The NOAEL concerning maternal and reproduction toxicity was 50 ppm, corresponding to 3.3-5.3 mg/kg bw per day.

In a 2-generation study, rats were dosed with 0, 10, 60, or 360 ppm in the diet. The test substance produced changes in the pancreas, adrenals, liver, kidney and bones from 10 ppm. The parental LOAEL was retained as 10 ppm, corresponding to 1.0 mg/kg bw for males and 1.1 mg/kg bw for females. The NOAEL for reproductive parameters is 60 ppm (4.3 mg/kg bw due to a decrease in implantation sites, litter size and in number of pups/litters born at 360 ppm). The offspring NOEL is 10 ppm (0.8 mg/kg bw) due to effects on the spleen and decrease in thymus weights at 60 ppm.

Toltrazuril

A 2-generation study in rats receiving toltrazuril in their diet at doses of approximately 0, 0.3, 1.25 and 5 mg/kg bw/day showed that the number of stillborn pups was increased in all treated groups, the statistical significance being only observed for the highest dosage and for the first generation of the lowest dose group. Due to these equivocal results, 0.3 mg/kg bw/day was retained as a LOEL.

Embryotoxicity / foetotoxicity, including teratogenicity

Emodepside

In rats, both ovarian weight and the gestation rate were unaffected by treatment. Clinical signs of systemic maternal toxicity were evident at dose rates of 6 mg/kg bw and above. Overall, severe maternal toxicity at 18 mg/kg bw resulted in adverse effects on foetal development. The NOEL for maternal toxicity was 2 mg/kg bw and the NOEL for developmental toxicity was 0.5 mg/kg bw.

In rabbits, the effects were similar to the rat studies. The NOEL for developmental toxicity was 5 mg/kg bw and the NOEL for maternal toxicity was lower than 5 mg/kg bw.

Toltrazuril

Two teratogenicity studies were performed in rats. In the first study, Wistar strain rats received toltrazuril at doses of 0, 3, 10, 30 mg/kg bw/day (in a tylose suspension) and 0 and 1 mg/kg bw/day (in supplemental study). Teratogenicity and embryotoxicity, such as dysplasia of long bones, hydrops, cleft palate, microphthalmia were observed at the highest dose. When compared to the controls, a statistical decrease in the number of live foetuses was reported at doses of 3 and 10 mg/kg bw/day. As only a slight increase in resorption was seen at 1 mg/kg bw/day, a LOEL of 1 mg/kg bw/day was retained from this study.

In a second study, rats were given 0, 1,3,10 and 30 mg/kg bw/day toltrazuril (using carboxymethylcellulose as suspending agent). In this study, NOELs of 3 mg/kg bw/day and 10 mg/kg bw/day were retained for maternotoxicity and embryotoxicity.

Two other teratogenicity studies were conducted in rabbits. In the first study, the rabbits received toltrazuril at doses of 0, 1, 3 and 10 mg/kg bw/day. Significant increases in the number of abortions were reported at 3 and 10 mg/kg bw/day. As three litters showed runts at the lowest level, no NOEL was retained.

In the second rabbit study, doses of 0, 0.5, 0.75, 1 and 2 mg/kg bw/day toltrazuril were given. At 2 mg/kg bw/day a significantly increased number of fused sternebrae was reported. As significant increases in placental weights were reported at 0.75 mg/kg bw/day and 1 mg/kg bw/day, the lowest dose 0.5 mg/kg bw/day was retained as the NOEL.

Mutagenicity / genotoxicity

Both emodepside and toltrazuril, as well as the major metabolite of toltrazuril, ponazuril, have been tested in a battery of *in vitro* and *in vivo* tests for genotoxicity. They are all considered non-genotoxic.

Carcinogenicity

Emodepside

No carcinogenicity studies have been performed on emodepside. Based on the negative results in the genotoxicity studies and the lack of structural alerts for this family of compounds the lack of carcinogenicity studies is acceptable.

Toltrazuril

Carcinogenicity studies were performed in mice (approximately 0, 2, 6, 18 mg/kg bw/day) and in rats (approximately 0, 1, 3, 10 mg/kg bw/day).

In mice, toltrazuril showed equivocal results as the significant increased incidence of lymphomas reported in males treated at the highest dosage was within the historical range of spontaneous rates (18% in males, 2% in control and 0 to 33% in the historical controls). The increased incidence of lymphomas in females (34% in treated animals, 22% in control) was just above the upper limits of historical control (33%) and was not significant.

In female rats, toltrazuril increased the incidence of endometrial adenocarcinomas significantly at the highest dosage (23/50 at 10 mg/kg bw/day; 6/50, 4/50 and 8/50 at 0, 1 and 3 mg/kg bw/day). At the highest dose, a reduction in the number of mammary tumours and hyperplasias in the pituitary was noticed in these rats. However, considering the significant increase in total incidence of pre-neoplastic and neoplastic lesions of the uterus for the two highest dosages (45 and 37 at 10 and 3 mg/kg bw/day versus 14 and 13 in the lowest and control groups) 3 mg/kg bw/day was retained as the threshold level for neoplastic tumours, while 1 mg/kg bw/day was retained as the threshold dose for tumour promotion, i.e., pre-neoplastic lesions. An imbalance in the female hormone system was suggested being involved in this tumourigen mechanism.

Studies of other effects

Skin and eye irritation and skin sensitization

Emodepside

In rabbits, emodepside was found to be non-irritating (patch test) to the skin and found not to be acutely irritating (instillation into conjunctival sac) to the eye. In guinea pigs, emodepside was found to have no skin sensitization potential.

Toltrazuril

GLP-compliant studies were performed according to guidelines. In rabbits, toltrazuril was found to be non-irritating to the skin or eyes. In guinea pigs, toltrazuril was found not to be a skin sensitizer.

Endocrinology

Emodepside

A study for subchronic oral toxicity of emodepside in rats (hormone determination in female rats, feeding study for 28 weeks and 14 weeks recovery) was performed. Many of the toxicological findings were similar to previous studies. It was noteworthy that the reduced body weight gains did not correct during the recovery period. The potent effects of emodepside on endocrine function were observed during treatment, although hormone concentrations returned to normal during the recovery period. The influence of treatment on ovarian function included increased numbers of corpora lutea and persistent oestrus, although the high dose rate is well above the recommended target dose for the dog. Oestradiol levels were reduced (if in persistent oestrus) and progesterone levels were not increased (if high numbers of corpora lutea). From the data on thyroid hormones, the administration of emodepside in rats at the highest dose is noted to suppress the total T3 level, in both a time- and dose-dependent manner, with a tendency towards increased T4 and TSH hormone levels.

The above study also included a review of the results of three additional *in vitro* studies investigating the effects of emodepside on sex steroid receptors, which indicated that emodepside had no effects or affinity for the receptors concerned.

A new subchronic oral toxicity study in female rats was performed to highlight possible secondary effects on the diabetic-like effects induced by emodepside. The effects seen were similar to previous studies, and together with results from gene expression studies in ovaries, liver and white adipose tissue, are in line with the hypothesis that emodepside induce a diabetes type-I like reaction without any direct effect on sexual hormone systems.

Toltrazuril

Toltrazuril and its metabolite ponazuril were tested for (anti)estrogenic and (anti)androgenic effects *in vitro* using receptor binding assays and two reporter cell lines, MVLN and PALM. The results showed no activity.

Studies on formulation

Acute toxicity

Single dose acute toxicity in rats after oral and dermal administration of Procox at a dose of 2000 mg/kg bw, corresponding to 40 mg toltrazuril and 2 mg emodepside, was studied. The result showed low acute toxicity with no clinical signs or effects on bodyweight or organ changes.

Irritation and sensitisation

Before testing irritation *in vivo*, an *in vitro* corrosion test was performed and gave a negative result. In rabbits the formulation was found to be non-irritating to the skin and eyes.

A skin sensitization test was performed in guinea pigs according to the Maximization test of Magnusson and Kligman. It showed that the formulation was not sensitizing.

Skin penetration

Dermal penetration was tested using rat and human skin *in vitro.* Emodepside and toltrazuril did not penetrate to any detectable amount through human skin. This is different to rat skin, where the absorbed dose was 0.02% emodepside and 0.27% toltrazuril. Some amount was found in the skin (dermal delivery). This amount was 0.21% emodepside and 0.34% toltrazuril in human skin and 8.56% emodepside and 5.84% toltrazuril in rat skin.

Microbiological properties

Toltrazuril

No antibacterial activity of toltrazuril was evident at concentrations of up to 128 µg/ml on *E. Coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or *Streptococcus pyogenes*. The MIC values of toltrazuril against *Trichophyton mengrophytes* and *Microsporum canis* ranged from 4 and 64 mg/l. No activity was found against *Candida albicans*, *Aspergillus fumigatus* and *Penicillium communis*.

User safety

A user safety risk assessment has been performed in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary products (EMEA/CVMP/543/03-FINAL). Worst case assumptions were based on dermal contact for professionals and non-professionals, and also for accidental oral ingestion by children. The risk to professional or non-professional users from handling or administering the product in accordance with the instructions in the SPC or package leaflet is low, with safety margins above 100. Accidental ingestion by children can be a risk, but is reduced by the child resistant closure of the bottle and also by the inclusion of relevant user safety warnings in the SPC, leaflet and on the outer carton.

Environmental safety

An environmental risk assessment is performed according to the relevant guideline (CVMP/VICH/592/98-Final). Since the product will be used in non-food animals only the risk assessment ends at Phase I. Based on the data provided the product is not expected to pose a risk for the environment when used in accordance with the instructions in the SPC/package leaflet, however due to the toxicity of emodepside to *Daphnia spp.* (water fleas), the following precaution has been included in the SPC and package leaflet: "*The product should not be allowed to enter water courses as this may be dangerous for fish and other aquatic organisms.*" Appropriate standard disposal advice for unused or waste product is also included in the SPC and package leaflet.

Overall conclusions on safety

Emodepside has previously been assessed by the CVMP and the data submitted in this application gives no indication of any alteration in its safety profile. The molecule has low acute toxicity by a variety of routes. The effects shown in oral repeated dose studies in rats and mice include reduction in weight gain, effects on neurological function, behaviour and respiration; reduction in the absolute weight of the testes; increase in the relative weight of the brain in male rats; ataxia; increased motility; piloerection; increase in glucagon-secreting cells with a trend towards significant hyperglycaemia; polydipsia and polyphagia. The liver, adrenal glands, pancreas and reproductive system were the principal target organs for toxicity. Not all changes were reversible after a 4 week recovery period. Developmental toxicity studies identified adverse effects in rats and rabbits. Reproductive parameters were affected only at levels with maternal toxicity. Emodepside is not genotoxic. Based on the negative results in the genotoxicity studies and the lack of structural alerts for this family of compounds the lack of carcinogenicity studies is acceptable. Emodepside is non-irritating to the eyes and skin and does not appear to be a skin sensitising agent.

Toltrazuril has been previously assessed by the CVMP for the purpose of setting an MRL. Its acute oral toxicity is low. In repeated dose studies in rats, their weight gain and daily food intake were decreased. Slight effects on haematological parameters and disturbances of the liver function were also observed. Dogs showed a general toxicity in the form of a reduction of feed and water intake and in bodyweight development. A reduction of testes and prostate organ weights were also observed. An increase in the weight of the heart was seen but without any histological changes or circulatory disturbances. Toltrazuril is considered non-mutagenic. In the two-generation study in rats the number of stillborn pups was increased with an equivocal statistical significance. In the developmental studies, two studies in rats showed very different effect levels. A decrease in the number of live foetuses and increase in resorptions were seen. Dysplasia of long bones, hydrops, cleft palate and microphthalmia were only observed at the highest dose. In rabbits, increased numbers of fused sternebrae, and increases of placental weights and runts were observed. In the carcinogenicity study in rats, an increased incidence of uterine tumours was seen in females. An imbalance in the female hormone system was suggested as being involved in the mechanism. The findings were regarded as rat-specific. Toltrazuril is not irritating to the skin or eyes and is not a skin sensitizer.

Studies on the main metabolite, ponazuril, showed that it is less toxic than the parent compound (toltrazuril).

Studies on the combination of both active substances (emodepside and toltrazuril) showed no evidence of interactions or synergistic effects. The acute toxicity was low. In the repeated dose studies similar effects were seen at similar levels to the individual active substances. The final formulation was not irritating to the skin or eyes and was not a skin sensitizer. Dermal penetration studies *in vitro* showed that emodepside and toltrazuril did not penetrate to any detectable amount through human skin.

A user safety risk assessment has been performed according to the CVMP User Safety Guideline (EMEA/CVMP/543/03-FINAL). The risk to professional or non-professional users from handling or administering Procox is low when used in accordance with the SPC/package leaflet. Accidental ingestion by children could be a risk, but is mitigated by the child resistant closures and appropriate warnings in the SPC, package leaflet and also on the outer carton.

The Environmental Impact Assessment for Procox stopped in Phase I and the product does not present any risk of concern to the environment. Standard disposal advice for unused or waste product is given in both the SPC and package leaflet.

4. Efficacy assessment

Pharmacodynamics

Emodepside is active against nematodes and is responsible for the activity of Procox against *Toxocara canis*, *Ancylostoma caninum* and *Uncinaria stenocephala*. Emodepside acts presynaptically in nematodes at the neuromuscular junction where it attaches to a latrophilin-like receptor initiating a cascade of events resulting in inhibition of pharyngeal pumping and locomotion of the nematode. Emodepside also acts via the Ca^{++}-activated K^{+} channel causing inhibition of feeding and locomotion of the nematode. The end result is flaccid paralysis and death of the nematode. Emodepside has nematocidal activity but lacks any cestocidal activity. There is no indication that it has anticoccidial activity.

Toltrazuril is active against *Eimeria* and *Isospora* species and responsible for the activity of Procox against *Isospora canis* and *Isospora ohioensis* complex. Toltrazuril is coccidiocidal rather than coccidiostatic, and is active against intracellular stages of coccidial parasites undergoing asexual or sexual reproduction. It is considered likely that toltrazuril interferes with respiratory-associated enzymes since it has an inhibitory effect on the activity of enzymes associated with the respiratory chain, such as NADH oxidase and succinate oxidase in mammalian host cells.

Development of resistance

No information regarding resistance of any parasites against emodepside or toltrazuril is available to date. The use of both active substances is recent or new in dogs. Emodepside has been authorised for use in dogs in a combination with praziquantel (Profender) only since 2008, but toltrazuril has not to date been authorised for use in dogs, although it has been available for the treatment of poultry, cattle, sheep and pigs for over 20 years. To avoid overuse of the product and thereby unnecessary risks for resistance, detailed information on prudent use has been included in the SPC (and package leaflet).

Pharmacokinetics

Basic pharmacokinetic properties of emodepside in the target species are described in Section 3 (Safety assessment). In summary, emodepside is highly protein bound in plasma (>99%) and it is also taken up into erythrocytes. The absorption of emodepside appears to be dependent on the formulation (vehicle) used. However there are no ADME studies performed in dogs for either emodepside or toltrazuril and therefore conclusions on the main elimination pathways in the target species cannot be concluded, although metabolism is indicated to be of importance for both substances (based on studies in other species and the available data following treatment with Procox oral suspension). Furthermore, there are no pharmacokinetic data in the target population, i.e., 2 week old dogs. However results from target animal safety studies with Procox oral suspension indicate that possible differences in exposure in young dogs do not result in clinically relevant adverse events following treatment.

Data submitted comprise systemic exposure levels of emodepside, toltrazuril, toltrazuril sulphoxide and toltrazuril sulphone, following single and repeated oral dosing using the marketing formulation at the proposed dose level in Beagle dogs (11-12 months old). Single doses of dose levels ranging from 0.5x to 2x the proposed therapeutic dose level did not reveal any major deviation from dose proportionality. Maximum emodepside concentrations of 39 μg/ml were reached 2 hours after the first dose and a fairly short half-life of 10 hours was estimated. Emodepside was therefore cleared from the systemic circulation between the repeated doses. However, all the toltrazuril entities exhibited very high systemic exposures, reaching maximum concentrations following the first dose of 17.28, 4.152 and

4.531 mg/ml for toltrazuril, toltrazuril sulphoxide and toltrazuril sulphone, respectively. Maximum concentrations were reached late, at 18, 103 and 264 hours post-dose. Based on this latter information, and the shape of the serum concentration versus time curve, entero-hepatic and/or coprophagia are suspected for all three entities. The half-life for toltrazuril is estimated to be 5 to 6 days. Little accumulation was observed following repeated dosing every two weeks for all entities except toltrazuril sulphone, where the accumulation was 3- to 4-fold.

A small study exploring the effect of concomitant food intake in adult Beagle dogs revealed an increased variability in systemic exposure following food intake, especially for emodepside. Due to the large variability and the low number of dogs studied the results are not completely conclusive, but the data did suggest no dramatic effect of feeding status on either emodepside or toltrazuril, except that the peak concentrations of emodepside appeared to be slightly lower when dogs were in the fed state. Therefore it was not necessary to include any recommendations in the SPC and package leaflet regarding administration of the product with food, or only to fasted dogs.

Dose determination / justification

Throughout the dossier, evaluation of the efficacy against nematodes was based on the reduction of parasite burden and was performed in accordance with the relevant VICH guidelines. Determination of the efficacy of treatment of *Isospora* infection was performed according to similar methods and was based on the reduction of parasite burden, as determined by number of oocysts in the faeces.

Four preliminary studies, using preliminary formulations, were conducted to identify an effective dose of emodepside against *T. canis*, *A. caninum* and *U. stenocephala*. *T. canis* was considered the most important nematode for young dogs, and as the formulation was also intended for efficacy against immature stages of *T. canis* (where data from the preliminary studies indicated that a slightly higher dose was needed), *T. canis* was selected as the dose limiting nematode. A pivotal dose determination study for emodepside was therefore performed with *T. canis* infection. In this study, a satisfactory efficacy of emodepside was demonstrated against adult *T. canis* at all the concentrations tested (0.225, 0.45 and 0.9 mg emodepside/kg) and the efficacy at the recommended target dose (0.45 mg/kg) was 100%.

In the dose determination studies with *Isospora* infection, difficulties were encountered in establishing adequate infections and as a result only preliminary results were acquired. These indicated that at a dose of 10 mg/kg, toltrazuril could be effective against patent *I. ohioensis* complex infections. Dose titration was attempted, but the effect of dose could not be evaluated due to the large differences in faecal oocyst counts of the study groups at treatment. Regarding *I. canis*, only scarce preliminary data were collected and no dose titration was attempted. The dose determining step for toltrazuril was therefore unsatisfactory, but available data indicated efficacy at 9 mg/kg, and this was chosen as the recommended target dose and subsequently used in the dose confirmation studies.

A series of GCP-compliant dose confirmation studies were conducted for both nematodes and *Isospora* to determine the efficacy of the final formulation administered at the minimum recommended target dose. The criteria specified in VICH guideline GL7 (>90% efficacy against each nematode species/stage should be demonstrated in two dose confirming trials) were met for:

- *Toxocara canis* (L4, immature adult)
- *Ancylostoma caninum* (adult)
- *Uncinaria stenocephala* (adult)
- *Isospora ohioensis* complex
- *Isospora canis*

Efficacy of treatment is also claimed against the adult stage of *T. canis*. There were, however inadequate infections of the control groups in one dose confirming trial in support of this claim and conclusions could therefore not be drawn from this study. However, 100% efficacy against adult *T. canis* was demonstrated using the final formulation at the lowest recommended target dose in the pivotal GCP dose-determination study. In addition, *T. canis* larvae were used as the dose-limiting nematode, and since sufficient efficacy was demonstrated against these, corresponding efficacy against adult *T. canis* can be expected. The CVMP considered that sufficient evidence to justify the claim of efficacy against adult *T. canis* had been demonstrated.

The dose confirmation studies with *Isospora canis* and *Isospora ohioensis* complex demonstrated >90% efficacy (as reduction in the number of oocysts in the faeces after administration during the prepatent period) in two separate trials. The duration of effective treatment depended on the number of days when an adequate infection could be demonstrated in the control group. In addition, treatment during the prepatent period significantly reduced the frequency of diarrhoea and resulted in increased body weight gain compared to the controls.

With regard to the treatment of patent infections, >90% efficacy was demonstrated for toltrazuril against *I. canis* during days 1-4 after confirmed patency of infection in one trial, and against *I. ohioensis* complex during days 1-2 after confirmed patency in another trial. The requirement to demonstrate efficacy in two separate trials for each claim was therefore not achieved, mainly due to the inadequate level of infections in the control groups (which showed the difficulties in reproducing clinical disease caused by *Isospora* infection in experimental trials). This also highlighted that the natural course of patent *Isospora* infections in dogs is self limiting, and that treatment during this stage of the disease is less important than treatment during the prepatent period. In addition, neither the duration nor the severity of the diarrhoea appeared to be influenced by treatment of patent infections compared to controls. It was agreed that the clinical signs of *Isospora* infection cannot be eliminated completely due to the course of the infection, and that the main purpose of treatment for *Isospora* is to reduce, control and eliminate the infection in the group/kennel in order to prevent further spread of the disease and subsequent reinfection.

Oocyst shedding was generally reduced more rapidly in treated groups compared to the corresponding controls, regardless of the time of treatment, but as oocyst counts were also clearly and rapidly reduced in the control groups it indicated that the disease is self-limiting. Treatment with Procox is therefore justifiably indicated as one of the measures to be taken in order to control and eliminate infection in groups/kennels with known problems of mixed infections with both nematodes and *Isospora*.

Target animal safety

One pivotal GLP target animal safety (TAS) study and two supportive studies were performed using the final formulation, and in these no treatment related systemic adverse events were recorded, demonstrating a safety margin of at least 5 times the maximum recommended target dose, i.e., 2.7 mg emodepside + 54 mg toltrazuril per kg bw. Mild and transient digestive tract disorders were demonstrated in treated dogs, mainly mild faecal changes such as loose faeces or white matter in the faeces. These faecal changes could be attributed to the presence of sunflower oil in the test formulations and were considered minor. Evaluation of tolerance in the clinical trials (for the determination of efficacy) showed no treatment related adverse effects, indicating acceptable safety of the product in young dogs after a single administration of the recommended dose under field conditions.

Treatment with Procox is intended as a single administration, however, in accordance with the SPC/package leaflet, the administration may be repeated at 2 week intervals up to 5 times. In the

pivotal TAS study, treatment with the product was repeated 5 times at 2 week intervals, but no evaluation of tolerance beyond this period of time was performed. In addition, data from kinetic studies in one year old dogs indicate that the systemic exposure of toltrazuril and toltrazuril metabolites is considerable, and that at least one of the metabolites appears to accumulate over time with repeated administrations. Data on systemic exposure are not available in the target population, i.e., 2 week old pups. The recommendation for repeated treatment is however justified with regard to the safety and systemic exposure of emodepside, toltrazuril, and toltrazuril metabolites in young dogs, since no adverse reactions were demonstrated in the target animal study. Furthermore, the Committee considered it unlikely that treatment with the product would be administered up to the specified maximum of 5 times.

No safety study was performed using either of the active substances alone, and no kinetic data on interactions in the target animal species were provided. Although not strictly in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), there was no indication of any interactions between the two active substances from either the preclinical studies, or the pivotal target animal safety study (performed with the final product formulation). It was therefore considered that sufficient data on target animal safety had been presented for the combination.

Emodepside is included in combination with praziquantel in a previously EU authorised product for the treatment of nematode and cestode infections in dogs (Profender tablets). There was some discrepancy in the frequency of adverse events between the safety studies performed with Procox and those performed with Profender tablets. When Profender tablets were administered to 9-14 weeks old dogs, neurological signs were recorded in the 3x and 5x dose groups. In Procox oral suspension the dose of emodepside is approximately 50% lower than in Profender tablets, and no neurological signs were observed in the Procox safety studies, even at 14x the recommended dose. Since the puppies in the pivotal Procox TAS study were not weaned their feeding status at treatment was unclear, however it can be assumed that the dogs were treated under fed conditions (since this would be normal feeding behaviour in such young dogs). The total absence of adverse reactions in the study indicates that feeding status, in contrast to Profender tablets, is not critical with regard to safety when Procox is administered to young dogs. This was further supported by data from a pharmacokinetic study which evaluated the effect of feeding status. In the clinical efficacy and field trials, a large number of dogs were treated with the recommended target dose and no adverse events were recorded. In these trials, feeding status varied between dogs, but a majority of animals in the field trials were fed within 4 hours of treatment.

The safety margin for emodepside has been demonstrated to be lower in dogs with homozygous mutation of the *mdr1* (multi drug resistance protein) allele which is responsible for avermectin sensitivity. Homozygous mutation is found primarily in dogs of Collie and related breeds. No studies to evaluate the safety of emodepside + toltrazuril in young *mdr1*-/- mutant dogs were presented, and in the previous evaluation of Profender tablets it was demonstrated that the safety margin in adult *mdr1*-/- dogs was lower than in non-mutant dogs. Since the recommended target dose for emodepside in Procox is considerably lower than for Profender tablets, it is likely that the safety margin is even greater for *mdr1*-/- dogs, but in the case of Procox, considerably younger animals are intended for treatment. In the studies evaluating the safety of emodepside in *mdr1*-/- mutant dogs, the animals included were adults, whereas in the case of Procox, dogs as young as 2 weeks are intended for treatment. It is unclear whether there is an increased risk of adverse events at treatment of very young *mdr1*-/- dogs with emodepside and treatment with Procox is therefore not recommended in these animals and the SPC/leaflet includes appropriate warnings to this effect.

Procox is intended for treatment of very young dogs, from 2 weeks of age and at least 0.4 kg bodyweight based on dogs included in the studies representing the lowest age category and body weight.

Field trials

To confirm the efficacy and safety of Procox under field conditions, three multicentre GCP field trials were carried out at different locations across Europe (Albania, Croatia, France, Germany, Hungary, Ireland, Portugal and Spain) and these were considered representative of the current epidemiological situation.

The efficacy against nematode infections was evaluated in a study involving 137 client owned dogs with diagnosed nematode infections. Non-inferiority was tested against a positive control product containing milbemycin oxime and praziquantel. Efficacy was evaluated as the reduction in number of nematode eggs in the faeces on day 10±3 after treatment, and superiority was demonstrated for Procox compared to the control product.

The efficacy against *Isospora* infections was evaluated in a study including 78 client owned dogs with diagnosed *Isospora* infections. Non-inferiority was tested against a positive control product containing sulfadimethoxine. Efficacy was evaluated as the reduction in number of oocysts in the faeces on days 3, 7 and 9±1 after treatment, and superiority was demonstrated for Procox compared to the control product on these days. Parameters determining the clinical relevance of the treatments, such as the reduction of diarrhoea and the effect on weight gain, or the impact on spread of infection, were not evaluated. The number of dogs infected with *I. canis* in the trial was low (5 dogs), which reflects the epidemiological situation. Extrapolation of data between *Isospora* species with regard to the efficacy of treatment with toltrazuril was considered possible, since there is no relevant difference between *I. ohioensis* complex and *I. canis* in their susceptibility to toltrazuril.

The efficacy of the prophylactic treatment of *Isospora* infection during pre-patency was evaluated in a placebo controlled field trial which included 80 client owned uninfected dogs from kennels with a history of *Isospora* infection. The primary efficacy criterion was the level of oocyst counts in the faeces on days 3, 7 and 9±1 after treatment, and the treatment was regarded as effective if the faecal oocyst count of treated animals was less than 80% of that in the control group. Superiority over placebo was demonstrated for the treatment with regard to the criteria set, and the faecal oocyst count of the treated animals was less than 5% of those in the control group, however the clinical relevance of the results and the impact of treatment on the control of infection were unclear since no dog developed the clinical disease, regardless of whether it received the treatment or the placebo.

The acceptance of the product was generally good.

The incidence of dogs harbouring mixed nematode and *Isospora* infections in the clinical field trials is unclear. It appears that mixed infections do occur in considerable numbers, especially in environments where many dogs are kept in confined areas, but the frequencies reported vary, and there is not enough information to conclude on their prevalence in the overall canine population in Europe.

Overall conclusions on efficacy

There was no apparent effect of food on the systemic exposure of either emodepside or toltrazuril apart from on the peak emodepside concentration, which appeared to be slightly lower after administration to fed dogs. Furthermore, concomitant food intake resulted in an increased variability in systemic exposure, especially for emodepside. No recommendation to dose the product either with food or to dogs in the fasted state is therefore necessary.

The available data on systemic exposure were collected in Beagle dogs of 11 months or older, so there are no pharmacokinetic data in the target population, that is, 2 week old dogs. However, provided that absorption is not compromised in such puppies, it is considered likely that the systemic exposure in the target population (given the same dose per kg body weight) is higher than for the studied adult dogs, as the eliminating organs are still maturing in the puppies/young dogs. It is, however, unlikely that this will have any clinically relevant effects.

A safety margin of at least 5 times the recommended target dose has been demonstrated in the target animal tolerance studies. Safety of the recommended target dose has also been demonstrated after up to a maximum of 5 separate doses, with a two week interval between each of the treatments. The lowest recommended age and weight of dogs recommended for treatment is 2 weeks and 0.4 kg respectively, and treatment of young *mdr1-/-* mutant dogs with this product is not recommended. Appropriate advice is included in the SPC and package leaflet to this effect.

The efficacy of treatment with the recommended target dose of the product (0.45 mg emodepside/kg and 9 mg toltrazuril/kg) was confirmed with regard to:

- *Toxocara canis* (L4, immature adult, adult)
- *Ancylostoma caninum* (adult)
- *Uncinaria stenocephala* (adult)
- *Isospora ohioensis* complex
- *Isospora canis*

Although the efficacy results against *I. canis* were limited in the field trials, due to the low numbers of infected dogs, the efficacy data for treatment with toltrazuril can be extrapolated between different *Isospora* species.

The primary purpose of treatment of *Isospora* infections is to reduce, control and eliminate infection in groups/kennels which have known problems with mixed nematode and *Isospora* infections in order to prevent spread of the disease and subsequent reinfection. Treatment with Procox is one of several measures included in such a control strategy.

The combination of the two active substances emodepside and toltrazuril in this product, and the use of Procox for treatment are justified when mixed infections with nematodes and *Isospora* have been suspected or demonstrated.

When no treatment against *Isospora* is indicated, an alternative product should be used for the routine prevention and/or treatment of nematode infections in puppies.

5. Benefit risk assessment

Introduction

Procox is a non-aqueous (oily) oral suspension for dogs which contains a fixed combination of two active substances, emodepside and toltrazuril, and is for the treatment of concurrent nematode and *Isospora* infections in young dogs. Emodepside is a known active substance which is included in an EU centrally authorised veterinary medicinal product. Although toltrazuril is a well established active substance in the EU in veterinary medicinal products it has not previously been authorised for use in dogs within the EU. The product has the following indications:

> *For dogs, when mixed parasitic infections caused by roundworms and coccidia of the following species are suspected or demonstrated:*
>
> *Roundworms (Nematodes):*
> - *Toxocara canis (mature adult, immature adult, L4)*
> - *Uncinaria stenocephala (mature adult)*
> - *Ancylostoma caninum (mature adult)*
>
> *Coccidia:*
> - *Isospora ohioensis complex*
> - *Isospora canis*
>
> *Procox is effective against the replication of Isospora and also against the shedding of oocysts. Although treatment will reduce the spread of infection, it will not be effective against the clinical signs of infection in already infected animals.*

Benefit assessment

Direct therapeutic benefit

Emodepside is active against nematodes and the efficacy of Procox has been demonstrated in clinical studies under EU-field conditions against adult and larval stages of *Toxocara canis*, adult *Uncinaria stenocephala* and adult *Ancylostoma caninum*. The mode of action is by the induction of flaccid paralysis and subsequent death of nematodes, initiated by attachment to presynaptic receptors in the neuromuscular junction.

Toltrazuril is active against coccidia, and the efficacy of Procox against infection with *I. ohioensis* complex and *I. canis* has been demonstrated under EU-field conditions. Toltrazuril is coccidiocidal and is active against the intracellular stages of coccidial parasites undergoing asexual or sexual reproduction.

The combination of emodepside and toltrazuril is justified in cases where mixed nematode and *Isospora* infections have been suspected or demonstrated.

Additional benefits

The pharmaceutical form (oral suspension) is suitable for treatment of puppies.

Risk assessment

The risk to professional or non-professional users from handling or administering Procox is low when used in accordance with the SPC/package leaflet. Accidental ingestion by children could be a risk, but

is mitigated by the bottles' child resistant closures and the user safety warnings in the SPC, leaflet and also on the outer carton.

The Environmental Impact Assessment for Procox stopped in Phase I and the product does not present any concerns for risk to the environment.

Acceptable tolerance after repeated administration was demonstrated when 5 separate administrations were given at two week intervals (the maximum recommended). The systemic exposure of emodepside, toltrazuril and toltrazuril metabolites in young dogs is unlikely to result in clinically relevant adverse reactions. The lowest recommended age and weight of dogs intended for treatment are 2 weeks and 0.4 kg respectively, representing the animals included in clinical trials. Since there is no information on the possible risks of treating young *mdr1-/-* mutant dogs with emodepside, treatment with Procox is not recommended in such animals and appropriate warnings to this effect are included in the SPC/leaflet.

No information regarding resistance of any parasites against emodepside or toltrazuril is available to date. To avoid overuse of the product and thereby unnecessary risks for resistance, satisfactory detailed information on prudent use has been included in the SPC and package leaflet.

Risk management or mitigation measures

In order to ensure the safe and effective use of Procox, specific and appropriate information and warnings are included in the SPC and package leaflet.

Evaluation of the benefit risk balance

The claims for efficacy against nematodes and *Isospora* infections have been adequately addressed and demonstrated.

Procox is well tolerated by the target animals. It also presents a low risk for users and the environment.

Appropriate information and warning statements are included in the product literature to ensure the safe and correct use of the product.

Procox oral suspension for dogs is considered to have a positive benefit-risk balance.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary use (CVMP) concluded that the quality, safety and efficacy of Procox were considered to be in accordance with the requirements of Directive 2001/82/EC as amended, and that the benefit-risk balance was favourable.