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Veterinary Medicines and Product Data Management

EPAR for Procox

Type II variation (EMEA/V/C/002006/II/0006)

Scope of the variation:
Addition of a therapeutic indication for the treatment of *Trichuris vulpis* (mature adults)

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

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1. Background information on the variation

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Bayer Animal Health GmbH, submitted to the European Medicines Agency (the Agency) on 11 June 2012 an application for a type II variation for Procox.

Procox was granted a Community marketing authorisation on 20 April 2011.

Procox is an oral suspension which contains a fixed combination of two 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.

Scope of the variation

Type II variation to add a therapeutic indication for the treatment of *Trichuris vulpis* (mature adults).

Current	Proposed
SPC 4.2 Indications for use, specifying the target species 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. 5.1 Pharmacodynamic properties Emodepside is a semi-synthetic compound belonging to the chemical group of depsipeptides. It is active against roundworms (ascarids, hookworms and whipworms). In this product, emodepside is responsible for the efficacy against *Toxocara canis, Uncinaria stenocephala* and *Ancylostoma caninum*.	SPC 4.2 Indications for use, specifying the target species 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) **- *Trichuris vulpis* (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. 5.1 Pharmacodynamic properties Emodepside is a semi-synthetic compound belonging to the chemical group of depsipeptides. It is active against roundworms (ascarids, hookworms and whipworms). In this product, emodepside is responsible for the efficacy against *Toxocara canis, Uncinaria stenocephala,* ~~and~~ *Ancylostoma caninum* **and *Trichuris vulpis***. Corresponding sections of package leaflet are amended accordingly.

Documentation submitted

In accordance with the requirements laid down in Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder submitted the following documentation:

- Administrative data (application form, English version of the product literature).
- Addendum to the Efficacy Detailed and Critical Summary.
- Efficacy data: study reports of two previously submitted studies (for another product) and three new studies
- Literature references.

Changes to the dossier held by the European Medicines Agency

This variation relates to the following parts of the current dossier held by the Agency:

- Parts 1 (Administrative) and 4 (Efficacy)

Steps taken for the assessment of this variation

- The dossier was submitted on 11 June 2012.
- The procedure started on 16 June 2012.
- A list of questions (LoQ) was adopted on 13 September 2012
- Responses to the LoQ from the applicant were received on 14 September 2012.
- The CVMP adopted an opinion and CVMP assessment report on 8 November 2012.
- On 10 December 2012, the European Commission adopted a Commission Decision for this variation.

2. Scientific discussion

Introduction

Procox oral suspension for dogs contains two active substances, emodepside and toltrazuril, and is indicated for the treatment of concurrent nematode and *Isospora* infections in young dogs.

2.1.1. Pharmacology

The dose regimen proposed for the treatment of the new indication is the same as for the initially authorised indications. There is no change in formulation, and no new data concerning pharmacology has been submitted in this variation.

Since there is no change in the dose of Procox for the new indication, and no information of development of anthelmintic resistance has been communicated, no increased risk for resistance development as a result of this variation is foreseen.

2.1.2. Clinical

Two of the five studies provided with this application were included in the original marketing authorisation application for Procox. The assessment of these two studies has been included in this report, with information added specifically concerning *T. vulpis*.

Unless otherwise indicated, the studies have all been performed in accordance with the guidelines:

- VICH Topic GL7, Efficacy requirements for anthelmintics: overall guidelines
- VICG Topic GL19, Efficacy of anthelmintics: Specific recommendations for canines.

According to these guidelines, acceptable efficacy should be demonstrated in two dose confirmation studies fulfilling the following criteria:

1. Infection was adequate, i.e., for each individual stage of nematode a minimum of 6 dogs with at least 5 worms should be present in the control group
2. Significant statistical differences in parasite burden was demonstrated between treated group and control group
3. ≥90% efficacy expressed as reduction of the number of worms recovered at necropsy in the treated group compared to the control group according to:

$$\text{Efficacy (\% reduction)} = \frac{(N2-N1) \times 100}{N2}$$

N1=Geometric mean count of target parasite for treated group
N2=Geometric mean count of target parasite for control group

In critical tests efficacy was determined according to:

$$\%\ \text{Reduction} = \frac{A \times 100}{(A+B)}$$

A= Total number of each species expelled in the faeces (post-IVP administration)
B= Number of each species recovered at necropsy

2.1.2.1 (Previously assessed) GCP dose confirmation study to confirm the efficacy of Procox against mature stages of *Uncinaria stenocephala* infection in naturally infected dogs

A randomised, blinded, placebo controlled study design was used and 16 cross breed dogs (7 male, 9 female) aged 2 – 24 months were included in the study, performed in South Africa.

Animals were selected based on natural infection with *U. stenocephala* and natural infection with *T. vulpis* and were randomly assigned to two treatment groups. To ensure adequacy of infection with *U. stenocephala*, dogs were selected based on demonstration of at least 2 faecal egg counts of $\geq$ 200 eggs per gram (epg) between days -7 and -1. For other nematode species that did not meet the requirements for adequate infection in the control group but in individual animals of the treatment group, critical tests were performed in individual animals.

On Day 0 of the study, the first (control) group remained untreated and the second group were administered Procox at the recommended dose rate of 0.45 mg/kg bw emodepside and 9 mg/kg bw toltrazuril.

Total faeces were collected between day -3 and day 7.

Results and conclusions:

This study had been submitted in the original Procox application and used the final formulation. Data relating to *T. vulpis* (a claim against which was not included in the original application) has now been included and only results pertaining to that parasite are discussed here.

Adequate infection was not demonstrated for other nematode species, but critical tests performed in individual animals provided supportive evidence of efficacy against natural infection with *T. vulpis*. For the 5 dogs in the treatment group that had ≥5 adult *T. vulpis* in their faeces, the treatment efficacy was 100%. No treatment related adverse effects were noted.

Further discussion of the conclusions is provided in the study below.

2.1.2.2 (New) Study to provide additional information on the data obtained on the efficacy of Procox against natural infection of *Trichuris vulpis* in the dogs of the previous study

Results and conclusions:

An adequate infection (≥5 worms in at least 6 dogs) was present in the control group but not in the investigational product (IVP) group, where only 5 dogs had ≥5 worms (in faecal washouts). The distribution of worm counts in the control group was determined to be acceptable (the lower bound of the 95% CI (4.7) was greater than 10% of the geometric mean (1.91)) and the infection was thus considered adequate for determining efficacy in the IVP group. IVP treatment against adult *T. vulpis* was 100% effective in the 5 IVP treated dogs that were adequately infected.

The adult worm burden at necropsy of group 2 was significantly lower than the burden found in the placebo control group ($p = 0.0079$). Although VICH guidelines GL7 and GL19 require a minimum of 6 adequately infected animals in two separate studies in order to provide a sufficient basis for statistical analysis, it is acknowledged that in this study a clear and convincing treatment effect (100% in individual animals and statistically significant difference between groups) was seen in those animals that were adequately infected.

The selection of animals was not performed according to criteria for demonstrating effect of treatment against *T. vulpis*. It is, however, unlikely that it has influenced the results of this trial, similar results would have been expected in a trial designed for the purpose, and it is thus acceptable to use data as presented.

2.1.2.3 (New) GCP dose confirmation study to confirm the efficacy of Procox against mature *Trichuris vulpis* infection in naturally infected dogs

A randomised, blinded, placebo controlled study design was used and 20 cross breed dogs (4 male, 16 female) aged 4+ months were included in the study, performed in South Africa.

Animals were selected based on natural infection with *T. vulpis* and were randomly assigned to two treatment groups. To ensure adequacy of *T. vulpis* infection, dogs were selected based on demonstration of at least 2 faecal egg counts of $\geq$ 60 eggs per gram (epg) between days -7 and -1.

On Day 0 of the study, the first (control) group remained untreated and the second group were administered Procox at the recommended dose rate of 0.45 mg/kg bw emodepside and 9 mg/kg bw toltrazuril.

Total faeces were collected between day -3 and day 7.

Results and conclusions:

100% efficacy of 0.45 mg emodepside/kg against adult (not immature adult) *T. vulpis* was demonstrated.

Adverse events (loose faeces, mucus on faeces) reported were consistent with the adverse events previously described for Procox.

Both dose confirmation studies were performed in South Africa. No corresponding data is presented for European conditions.

2.1.2.4 (Previously assessed) GCP clinical field study to evaluate the efficacy and safety of Procox in dogs naturally infected with intestinal nematodes (*Ascarididae, Ancylostomidae)*

This controlled, blinded, blocked and randomized multicenter non-inferiority field trial involved 137 client owned dogs (of various breeds and aged 4+weeks) in 20 clinics in 5 European (3 EU) countries.

Animals were selected based on natural intestinal infection with confirmed by eggs in their faeces. The nematodes of interest were *T. canis*, *A. caninum* and *U. stenocephala* but were not limited to these. There were 40 dogs withdrawn from the study due to negative faecal egg counts for parasites of interest on day -1/0 or if there were >5 animals from the same kennel. In addition, the applicant included an additional population termed “extended PP” where all animals per kennel/owner were included. The ITT population was used for evaluation of safety as summarised in the section for target animal safety. In the original study 16 dogs with mixed nematode and coccidial infections were included, but the results with regard to nematode infections are analysed in this trial.

Dogs were randomly assigned to one of two treatment groups and administered the recommended dose of either the test product (minimum oral dose of 0.45 mg/kg bw emodepside and 9.0 mg/kg bw toltrazuril) or the control product (an EU authorised product containing milbemycin oxime and praziquantel; minimum oral dose of 0.5 mg/kg bw milbemycin oxime and 5.0 mg/kg bw praziquantel) on day 0.

Faecal samples were collected for determination of faecal egg counts (FEC) on day -1/0 and twice on day 10+3. The primary endpoint was the reduction in FEC on day 10±3 (mean of two samples) compared to baseline in all nematode species. The efficacy of the test product was assessed for non-inferiority by comparison of mean FEC on day 10±3 to the control group. The secondary endpoint was the reduction in FEC from baseline for the species *Ascarididae* and *Ancylostomidae*, separately.

Results and conclusions:

This multicenter GCP study was performed in the EU with the final formulation. This study was previously assessed in the application for marketing authorisation for Procox. Non-inferiority was shown for the test product compared to the control product in both populations (PP and extended PP). The reduction of FEC was significantly higher (superior) for the test product compared to the control product (p=0.0074, PP population). No treatment related adverse events were recorded.

The results are discussed in further detail in the study below.

2.1.2.5 (New) Evaluation of the efficacy and safety of Procox in dogs naturally infected with intestinal nematodes (*Trichuris vulpis*) in a clinical field study.

Addition to the final study report: (Previously assessed) GCP clinical field study to evaluate the efficacy and safety of Procox in dogs naturally infected with intestinal nematodes (*Ascarididae, Ancylostomidae)*

This study was a subgroup analysis of the GCP multicentre field study reported under 2.1.2.4. and included data from a total of 17 of the dogs, 11 in the IVP group and 6 in the control group, from a total of 6 study sites in 4 countries.

The primary endpoint was a reduction of FEC (percentage efficacy) on day 10±3 (mean of two samples) compared to baseline. In the absence of a negative control, reduction was calculated by comparing geometric mean counts of FEC post treatment to baseline. Mean FEC on day 10±3 was compared to the control group for non-inferiority.

Results and conclusions:

No differences in animal characteristics between treatment groups were identified that were considered to potentially have affected the outcome of the efficacy evaluation.

Non-inferiority to the comparator could not be demonstrated in this analysis but it is not surprising considering that it comprises only a part of the original population. However, a reduction in FEC of 98.94% post baseline was shown, and considering the absolute numbers of FEC a clear reduction is seen in both groups indicating a high degree of efficacy. The Committee therefore concluded that sufficient efficacy of treatment against *T. vulpis* in field conditions has been demonstrated.

Inclusion in the study was not made for the purpose of demonstrating efficacy against *T. vulpis*, but according to the statistical analyses performed to compare treatment groups, no imbalance between treatment groups that is expected to influence the result was shown.

2.2. Summary and Conclusions

The CVMP considered that data from the studies provided show a convincing degree of efficacy of treatment against *T. vulpis*, even though strictly speaking, the requirements in the sense of number of adequately infected animals in all studies have not been fulfilled. Convincing efficacy against *T. vulpis* was demonstrated in both dose confirmation studies as well as in the field trial. Inclusion of animals in the previously submitted studies was not originally designed for the purpose of demonstrating efficacy against *T. vulpis*, but there is no indication that this should influence the final result. Indeed, in the new dose confirmation study designed for this purpose (study 2.1.2.3) 100% efficacy was demonstrated.

Both dose confirmation studies were performed using naturally infected dogs in South Africa, and although no corresponding trial was performed with a European strain of *T. vulpis* the CVMP considered this justified as no European strains were available for the conduct of the second dose confirmation study. Furthermore, although experimental *T. vulpis* infections are possible they often fail to establish adequately thus complicating the maintenance of isolates and anthelmintic studies for this parasite.

The two dose confirmation studies in naturally infected dogs both demonstrated full 100% efficacy. The results of these studies were confirmed by the field study. In the field study, the analysis population of 17 dogs naturally infected with *T. vulpis* came from 6 different veterinary practices in 4 European (3 EU) countries which represented a good variety of geographical origins across Europe. An efficacy of 98.9% was observed.

Additional information on the efficacy of the active substance emodepside against *T. vulpis* was presented from previous data submitted and evaluated for the Profender tablet formulation (Profender tablets for dogs contain emodepside and praziquantel, and is a centrally authorised product from the same marketing authorisation holder). Information can be found in the EPAR for Profender: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/veterinary/000097/WC500063849.pdf

The Committee were reminded that the results of the studies for Profender did not suggest that the susceptibility of *T. vulpis* to emodepside varies geographically, moreover the South African isolate did not seem to be more susceptible to emodepside than US or European isolates. CVMP concluded that no relevant differences in the efficacy of Procox against *T. vulpis* originating from South Africa and Europe are to be expected and therefore that further dose confirmation studies were not warranted.

Since there are no changes in either the dose rate or the safety profile of Procox as a result of this variation the Committee agreed there was no reason to change its periodic safety update report (PSUR) cycle.

3. Benefit-risk assessment

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.

3.1. Benefit assessment

An adequate level of efficacy against *T. vulpis* has been demonstrated in dogs following treatment with Procox (emodepside and toltrazuril) at the recommended dose.

3.2. Risk assessment

There are no changes in the dose or safety profile made by this variation. Also no additional risk for the development of anthelmintic resistance is foreseen to result from this new indication.

3.3. Evaluation of the benefit-risk balance

No change to the impact on the environment is envisaged.

The benefit-risk balance compared to the assessment performed during the initial authorisation of this product, Procox, remains positive.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

4.1. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annexes I and IIIB