17 March 2016
EMA/230625/2016
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Profender (EMEA/V/C/000097/II/0032)

International non-proprietary name: Praziquantel/emodepside

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

Rapporteur: R. Breathnach

Co-rapporteur: M. Mendes

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the variation

1.1. Submission of the variation application

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

On 7 May 2015, the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on "Minor-Use-Minor-Species" (MUMS) are applicable to the assessment of the proposed indication against *Toxocara cati* (L_3 larvae) – treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring in cats.

1.1.1. Scope of the variation

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

The variation is to add the following therapeutic indications for Profender spot-on solution for cats:
- *Toxocara cati* (L3 larvae) - treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring
- *Dipylidium caninum* (immature adult)
- *Aelurostrongylus abstrusus* (adult)

Current	**Proposed**
SPC - Profender spot-on solution for cats (single pipettes & multi-dose bottle)	**SPC - Profender spot-on solution for cats (single pipettes & multi-dose bottle)**
4.2. Indications for use, specifying the target species	4.2. Indications for use, specifying the target species
For cats suffering from, or at risk from, mixed parasitic infections caused by roundworms and tapeworms of the following species:	For cats suffering from, or at risk from, mixed parasitic infections caused by roundworms ~~and~~, tapeworms **and** lungworms of the following species:
Roundworms (Nematodes) *Toxocara cati* (mature adult, immature adult, L4 and L3)	Roundworms (Nematodes) *Toxocara cati* (mature adult, immature adult, L4 and L3) ***Toxocara cati* (L3 larvae) - treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring**
Toxascaris leonina (mature adult, immature adult and L4) *Ancylostoma tubaeforme* (mature adult, immature adult and L4)	*Toxascaris leonina* (mature adult, immature adult and L4) *Ancylostoma tubaeforme* (mature adult, immature adult and L4)
Tapeworms (Cestodes) *Dipylidium caninum* (adult)	Tapeworms (Cestodes) *Dipylidium caninum* (**mature** adult **and immature adult)**
Taenia taeniaeformis (adult) *Echinococcus multilocularis* (adult)	*Taenia taeniaeformis* (adult) *Echinococcus multilocularis* (adult)

	Lungworms ***Aelurostrongylus abstrusus* (adult)**
4.9. Amounts to be administered and administration route ... A single administration per treatment is effective. ...	4.9. Amounts to be administered and administration route ... **For the treatment of roundworms and tapeworms** a single administration per treatment is effective. **For the treatment of queens to prevent lactogenic transmission of *Toxocara cati* (L_3 larvae) to the offspring, a single administration per treatment approximately seven days prior to expected parturition is effective.** **For the lungworm *Aelurostrongylus abstrusus*, two treatments administered two weeks apart are effective.** ... Corresponding sections of the labelling and package leaflet are amended accordingly. Local representatives' details have been updated.

2. Scientific discussion

In support of the indication (immature adult stages of *Dipylidium caninum*), the applicant has presented two dose confirmatory studies. One dose confirmatory study has been provided to support a new minor use indication (*Toxocara cati* (L3 larvae) - treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring. For *Aelurostrongylus abstrusus* (adult) indication, the applicant has presented two dose confirmatory studies and one field study. In addition, the user safety assessment was updated and a statement concerning the potential environmental impact was provided.

2.1. Safety assessment

2.1.1. User safety

No difference in risk to the user is foreseen for two of the newly proposed indications (*Toxocara cati* (L_3 larvae) and *Dipylidium caninum* (immature adult)), given that the product will be applied using the currently approved posology (single application). However, an updated user safety assessment was provided since the treatment of *Aelurostrongylus abstrusus* (adult) requires two administrations a fortnight apart, and thus increases the handling frequency of the product.

The applicant refered to toxicological data on emodepside and praziquantel previously submitted within the context of the initial marketing authorisation applications for Profender Spot-on for cats. Typical use scenarios were described for professional and non-professional users with potential dermal and oral route of exposures.

In order to characterise the risk during the application phase of the product when applied twice at an interval of a fortnight, the margin of exposure (MOE) was calculated for both active substances. Based upon the results of an *in-vitro* penetration assay, daily systemic exposures were estimated and compared with the NOAELs of emodepside and praziquantel. It could be accepted that the MOEs calculated for both substances exceed 100, suggesting an adequate margin of safety for the user.

In order to assess the user safety during the post-application phase, the applicant refers to the results of a 'Stroke test' which was previously reviewed by the CVMP as part of the original application for Profender. Calculations have been presented for dermal exposure (following both single and repeated application of the product) and oral exposure. In calculating MOEs, the applicant has referred to NOAELs for dermal exposure determined from repeated dose dermal toxicity studies in rats and rabbits and for oral exposure determined from a sub-acute (4 weeks) oral combination study in rats. It was concluded that the provided calculations can be considered a "worst case" scenario and that the administration of the product on two occasions a fortnight apart will not present an unacceptable risk to children from either dermal or oral exposure during the post-application phase i.e. from stroking/petting treated animals.

2.1.2. Environmental risk assessment

A statement was provided to address the potential impact of the increased frequency of application of the product in cats for the newly proposed indication against *Aelurostrongylus abstrusus*. It was concluded that application of the product on two occasions a fortnight apart (as opposed to a single application) would not change the existing conclusion in respect of environmental risk; that is, the product will not present an unacceptable risk for the environment.

2.2. Efficacy assessment

2.2.1. Proposed indication against Dipylidium caninum (immature adults) in cats.

The results of two controlled studies have been provided in support of the proposed indication. Both studies were randomised, blinded and GCP-compliant. In both studies, cats were artificially infected with *Dipylidium caninum* (by being orally or topically exposed to *D.caninum* infected fleas).

In the first study, 18 cross-bred cats were topically infested with 100 fleas (8 days before treatment) and then orally with 100 fleas mixed into cat food (5 days before treatment). On the designated treatment day, cats were either administered Profender Spot-on (n=9) at the minimum recommended treatment dose of 3 mg/kg emodepside and 12 mg/kg praziquantel (equivalent to 0.14 ml of per kg bodyweight) or administered placebo (control group, n=9). At necropsy (10 days after treatment), at least seven protoscoleces were recovered from the stomach and small intestines of 5 out of the 9 animals in the control group, with a further 2 animals having two protoscoleces. The applicant provided justification in support of the adequacy of artificial infection with reference to historical data, literature review and expert testimony. The CVMP accepted that the level of artificial infection achieved in this study was adequate for the purpose of investigating efficacy of Profender Spot-on against *D.caninum* (immature adults). Based on the findings of this study, the percentage effectiveness (comparative reduction in geometric mean counts) of Profender Spot-on was determined to be 92.6% with a statistically significant p-value of 0.025.

In the second study (designed similarly to the first), determination of efficacy was not possible as there was inadequate infection of cats with *D.caninum* (only 4 out 10 cats were infected with 1 to 3 protoscoleces).

Relevant guidelines (VICH GL20 – Efficacy of anthelmintics: specific recommendations for feline) recommend that two dose confirmatory studies with a minimum of 6 adequately infected animals (in both test and control groups) should be conducted to grant a claim. That said, it is acknowledged that the product is already approved for adult stages of *Dipylidium caninum*. On that basis, the CVMP agreed that only one suitably conducted dose confirmatory study was required.

The CVMP concluded that the findings from the first study are considered adequate to support the proposed indication.

2.2.2. Proposed indication against *Toxocara cati* (L3 larvae) - treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring.

The product is currently approved for use in cats suffering from, or at risk from, mixed parasitic infections with *Toxocara cati* (mature adult, immature adult, L4 and L3). In support of the proposed indication, the applicant has provided the results of a single study.

Relevant guidelines recommend that two dose confirmatory studies should be conducted to grant a claim. However, considering that the product is already approved for the treatment of mature adult, immature adult, L_4 and L_3 stages of *Toxocara cati* and that the proposed indication was classified by the CVMP as a 'minor use', one suitably conducted dose confirmatory study can be accepted.

The study provided is placebo-controlled, randomised, blinded and GCP-compliant. A total of 16 pregnant queens were orally infected with approximately 2,000 embryonated *Toxocara cati* per day for 10 days (during the final third of pregnancy). One day after last infection, the queens were randomised to treatment group and administered either Profender Spot-on (n=8) at the minimum recommended treatment dose of 3 mg/kg emodepside and 12 mg/kg praziquantel (equivalent to 0.14 ml of per kg bodyweight) or placebo

(n=8). Efficacy was assessed on day 56 post-partum on the basis of the necropsy worm count of one randomly chosen kitten from each litter. All 8 necropsied kittens from queens in the control group had at least 7 worms (range 7-72) and the infection was considered adequate for efficacy assessment.

Based upon the results of the study presented, it can be accepted that the product has an efficacy of greater than 98% against *T.cati* (L_3 larvae), when administered approximately 7 days prior to expected parturition.

2.2.3. Proposed indication against *Aelurostrongylus abstrusus*.

A total of four studies were provided to support the proposed indication. In addition to a pilot study aimed at establishing a model for artificial infection of cats, two dose confirmation studies and a field study were conducted.

The first dose confirmation study was a blinded, placebo-controlled study in which 8 artificially infected cats were administered the product on a single occasion. Results indicated a marked decrease in faecal larval output (>99%). However, an acceptable level of efficacy (>90%) against adult stages was not achieved.

In a second, blinded, placebo-controlled dose confirmation study, cats were artificially infected with *Aelurostrongylus abstrusus* L_3 larvae 43 days before first treatment (Day -43). Study animals were treated once on study day 0 and again on study day 14. Cats assigned to the test product group (n=8) received Profender Spot-on at a dosage of 3 mg/kg bodyweight emodepside and 12 mg/kg bodyweight praziquantel (corresponding to 0.14 ml spot-on formulation per kg bodyweight). Cats assigned to the control group (n=8) were treated with the control product at a dose of 0.1 ml/kg BW. Faeces were collected for faecal larval counts from all study cats on nine occasions up to Day 29 post-treatment. Necropsy was performed on study days 33-36 and worm burden in the lungs was determined. All eight cats in the control group were reported to be infected with *A. abstrusus* (5 - 95 worms per cat were found during necropsy (geometric mean 17.6)).
In this study, administration of the test item resulted in a marked decrease in faecal larval output (>99%). Results of this study confirmed effectiveness (>99% reduction in total worm count) of the product for the proposed indication (adult *A. abstrusus*) using the proposed posology (two applications, a fortnight apart).

The GCP-compliant positively-controlled field study investigated effectiveness in 12 naturally infected cats following single application of the product. Although a number of deficiencies with the study were noted, the results were considered to provide non-pivotal support for efficacy, given that a single treatment with Profender Spot-on resulted in a 99.38% reduction in faecal larval count relative to baseline.

While only one study confirmed adequate efficacy based on adult worm count (when the product is administered on two occasions, a fortnight apart), a marked reduction in faecal larval count was reported in all three studies, following administration of either one or two doses of the test item. It is noted that previously the CVMP accepted faecal larval counts as a primary efficacy parameter for the *A. abstrusus* indication.

Based on the totality of efficacy data presented, the CVMP accepted that the proposed indication against *A. abstrusus* indication has been adequately supported.

2.2.4. Target animal tolerance

The product will be applied at the same dose rate as currently approved for two of the three newly proposed indications (*Toxocara cati* (L_3 larvae) - treatment of queens during late pregnancy to prevent lactogenic

transmission to the offspring and *Dipylidium caninum* (immature adult)). Consequently, no difference in tolerance is to be expected for those indications.

Concerning the proposed indication against *Aelurostrongylus abstrusus*, it is proposed that the product be applied on two occasions, a fortnight apart. Previously submitted tolerance studies have investigated tolerance to the product following administration of doses of up to 10 x the recommended treatment dose (RTD) and following repeated administration at fortnightly intervals on up to 6 occasions. Based upon that data, the CVMP concluded that the product was generally well tolerated when administered at up to 10 x RTD and was well tolerated when administered repeatedly at two-week intervals for 6 occasions at doses up to 5 x RTD.

It was therefore concluded that the repeated application of the product (on two occasions, a fortnight apart) at 1 x RTD for the newly proposed indication against *Aelurostrongylus abstrusus* is not expected to present a risk in terms of target animal tolerance. This is further supported by the fact that an acceptable level of general tolerance was reported in the dose confirmation study investigating efficacy of the product when applied in accordance with the proposed posology.

3. Benefit-risk assessment

3.1. Benefit assessment

This variation application has been submitted for the purpose of introducing three new indications. It is proposed that the product be used against:

- *Toxocara cati* (L_3 larvae) - treatment of queens during late pregnancy to prevent lactogenic transmission to the offspring
- *Dipylidium caninum* (immature adult)
- *Aelurostrongylus abstrusus* (adult)

Consequently, the addition of new indications may be considered as providing additional benefit for the target species in terms of being able to treat conditions for which the product was not previously approved.

3.2. Risk assessment

The only amendment to the existing posology is the proposal to recommend an increased frequency of treatment for the indications against *Aelurostrongylus abstrusus* (two treatments, a fortnight apart). No new risks have been identified for the user, target animal or the environment in respect of this increased frequency of treatment application.

3.3. Evaluation of the benefit-risk balance

The newly proposed indications may be considered as providing additional benefit for the target species. In addition, it is accepted that the addition of these indications will not pose an increased risk to the target animal, the user or the environment. Therefore, the overall benefit/risk balance remains unchanged and can be considered 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 to the Community marketing authorisation: Annexes I, IIIA and IIIB.