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Committee for Medicinal Products for Veterinary Use

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Broadline Type II variation (EMEA/V/C/002700/II/0013)

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

1.1. Submission of the variation application(s)

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant), applied to the European Medicines Agency (the Agency) for changes to the marketing authorisation for Broadline.

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 proposed changes are to extend the spectrum of efficacy with the proposed addition of the following indications to the already approved for Broadline:

- treatment of infestations with cestodes *Joyeuxiella pasqualei* (adults), *Joyeuxiella fuhrmanni* (adults) and *Diplopylidium* spp.;
- treatment of infestation with the respiratory nematode *Troglostrongylus brevior* (L3, L4 and adults);
- reduction of the level of infestation with the trematode *Opisthorchis felineus*, the cat liver fluke.

Current	**Proposed**
SPC **4.2 Indications for use, specifying the target species** (...) Cestodes - Treatment of infestations with tapeworms (Dipylidium caninum, Taenia taeniaeformis, Echinococcus multilocularis). Nematodes (...) - Treatment of infestations with feline lungworm (L3 larvae, L4 larvae and adults of Aelurostrongylus abstrusus). (...) - Prevention of heartworm disease (Dirofilaria immitis larvae) for one month.	**SPC** **4.2 Indications for use, specifying the target species** (...) Cestodes - Treatment of infestations with tapeworms (Dipylidium caninum, Taenia taeniaeformis, Echinococcus multilocularis, **adult Joyeuxiella pasqualei, adult Joyeuxiella fuhrmanni, Diplopylidium spp.).** Nematodes (...) - Treatment of infestations with feline lungworms (L3 larvae, L4 larvae and adults of Aelurostrongylus abstrusus **and Troglostrongylus brevior)**. (...) - Prevention of heartworm disease (Dirofilaria immitis larvae) for one month. **In the context of mixed infestations, the product can additionally reduce the level of infestation with the cat liver fluke (Opisthorchis felineus).**

SPC: 5.1 Pharmacodynamic properties (...) Praziquantel is a synthetic isoquinoline-pyrazine derivative with activity against tapeworms. Praziquantel is rapidly adsorbed via the surface of the parasites and affects membrane permeability in cestodes, influencing divalent cation fluxes, particularly calcium ion homeostasis, which is thought to contribute to the rapid muscle contraction and vacuolisation. This results in severe damage to the parasite integument, contraction and paralysis, disruption of metabolism and finally leads to the death and expulsion of the parasite. Disintegrated and partially digested fragments may occasionally be seen in the faeces.	**SPC: 5.1 Pharmacodynamic properties** (...) Praziquantel is a synthetic isoquinoline-pyrazine derivative with activity against tapeworms. Praziquantel is rapidly adsorbed via the surface of the parasites and affects membrane permeability in cestodes, influencing divalent cation fluxes, particularly calcium ion homeostasis, which is thought to contribute to the rapid muscle contraction and vacuolisation. This results in severe damage to the parasite integument, contraction and paralysis, disruption of metabolism and finally leads to the death and expulsion of the parasite. Disintegrated and partially digested fragments may occasionally be seen in the faeces. **Praziquantel also demonstrates activity against some trematodes**.
PL **4. INDICATIONS** For cats with, or at risk from mixed infestations by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time. (…) Cestodes - Treatment of infestations with tapeworms (*Dipylidium caninum*, *Taenia taeniaeformis*, *Echinococcus multilocularis*, Nematodes - Treatment of infestations with gastrointestinal nematodes (……..). - Treatment of infestations with feline lungworm (L3 larvae, L4 larvae and adults of *Aelurostrongylus abstrusus*). - Treatment of infestations with vesical worms (*Capillaria plica*). - Prevention of heartworm disease (*Dirofilaria immitis* larvae) for one month.	**PL** **4. INDICATIONS** For cats with, or at risk from mixed infestations by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time. (…) Cestodes - Treatment of infestations with tapeworms (*Dipylidium caninum*, *Taenia taeniaeformis*, *Echinococcus multilocularis*, **adult *Joyeuxiella pasqualei*, adult *Joyeuxiella fuhrmanni, Diplopylidium spp.*)** Nematodes - Treatment of infestations with gastrointestinal nematodes (……). - Treatment of infestations with feline lungworms (L3 larvae, L4 larvae and adults of *Aelurostrongylus abstrusus* **and *Troglostrongylus brevior*).** - Treatment of infestations with vesical worms (*Capillaria plica*). - Prevention of heartworm disease (*Dirofilaria immitis* larvae) for one month. **In the context of mixed infestations, the product can additionally reduce the level of infestation with the cat liver fluke (*Opisthorchis felineus*).**

2. Scientific discussion

2.1. Introduction

Broadline is a spot-on solution for use in cats, which contains four active substances: fipronil, (S)-methoprene, eprinomectin and praziquantel. It is available in applicators of two different sizes (0.3 or 0.9 ml) corresponding to cats of different bodyweights. It is currently indicated to treat cats with, or at risk of, mixed infestations by cestodes, nematodes, and external parasites.

The proposed changes concern the addition of the following helminth species to the indications approved for Broadline: the cestodes *Joyeuxiella pasqualei* (adults), *Joyeuxiella fuhrmanni* (adults) and *Diplopylidium* spp., the respiratory nematode *Troglostrongylus brevior* (L3, L4 and adults), and the trematode *Opisthorchis felineus*, the cat liver fluke.

In support of the proposed changes, four recent laboratory dose confirmation studies were submitted. Those studies investigated the efficacy of Broadline based on worm counts; they were GCP-compliant and conducted in accordance with VICH GL7 (Efficacy of Anthelmintics: General Requirements; CVMP/VICH/832/99) and VICH GL20 (Specific recommendations for Feline).

2.1.1. MUMS/limited market status

The applicant requested classification of the new indications as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied during the assessment. MUMS/limited market status was granted based mainly on the overall low prevalence of the parasites in the EU and their localization (mainly restricted to Mediterranean countries, while *J. fuhrmanni* has not been described in Europe to date). In the case of *O. felineus*, the indirect zoonotic character of the infestation was considered an additional argument in favour of the MUMS status.

2.2. Efficacy data regarding the cestodes *(Joyeuxiella pasqualei, Joyeuxiella fuhrmanni,* and *Diplopylidium spp.)*

The three proposed cestode species belong to the family Dipylidiideae (formerly Dilepididae), as well as the more common *Dipylidium caninum*. The metacestodes are thought to develop in coleoptera as the first intermediate hosts, and second intermediate hosts are small reptiles (such as lizards and geckos). Cats become infested by ingesting the second intermediate host.

As for other cestodes, the effect of Broadline is due to the presence of praziquantel in the fixed combination product.

The demonstration of efficacy against dipylidiid cestodes does not include field data. This can be accepted in a context of minor use, given the overall low prevalence in Europe. The omission of a second dose confirmation study as generally required, and the fact that the studies submitted were conducted in the Middle East and not in Europe, was accepted based on the fact that the test cats were naturally infested, which is assumed to cover a range of different strains and host factors. Also, the established efficacy against *D. caninum*, and the submitted efficacy data against two different *Joyeuxiella* species were indicative of overall efficacy against dipylidiid cestodes.

2.2.1. Joyeuxiella (*J. pasqualei, J. fuhrmanni*)

One GCP-compliant dose confirmation study (PRD0315301) in naturally infested cats was presented in support of efficacy of a single topical treatment with Broadline at the minimum recommended dose of 0.12 ml/kg body weight on Day 0, topically, against natural infections with *J. pasqualei* and *J. fuhrmanni*. The study was performed in the United Arab Emirates (UAE) in 2015 and involved 13 treated animals and 13 untreated controls, with no epidemiological link. The cats were included in the study based on confirmed dipylidiid cestode infestation following faecal examination. Cats were euthanised at Day 7, and helminths were recovered and identified by their morphology.

The recorded efficacy percentages, based on geometric means, were 99.7% for adult *J. pasqualei*, and 100% for adult *J. fuhrmanni*, but only 69.8% for juvenile *Joyeuxiella* spp. The juvenile (immature) stage was defined by the impossibility to identify worms up to the species level. No adverse events or other health problems were observed throughout the study.

The CVMP accepted that that results support the efficacy of Broadline in the treatment of adult worms, but not for immature worms. However, as cats on the field might harbour a mixed population of immature and adult worms, and the proportion of immature worms may be high, possibly due to a particularly long life cycle, the overall efficacy may be insufficient to prevent the infestation from being fully cleared.

Therefore, the CVMP considered that a claim for efficacy in adult *Joyeuxiella* spp. is acceptable, but the user should be warned that the presence of a high number of immature worms may preclude complete eradication. The following warning was added to section 4.4: "*Some cats with patent Joyeuxiella spp. infestation may nevertheless harbour a high proportion of juvenile worms, which are not susceptible to the product; therefore a post-treatment follow-up is recommended in case of such infestations*."

2.2.2. *Diplopylidium* spp.

The applicant presented one laboratory dose confirmation study (PRD0248001) to determine the efficacy of a single topical treatment with Broadline at the anticipated minimum dose (0.12 ml/kg body weight on Day 0) in naturally infested cats.

The study was conducted in Qatar in 2012 and included 12 treated animals and 12 untreated controls, with no epidemiological link. This study was already provided with the initial MA application for Broadline; its objective was to test efficacy against *Taeniae taeniaeformis*, but the untreated control cats also revealed infestation to a sufficient level by *Diplopylidium* spp.

No adverse events or other health problems were observed throughout the study.

While recorded efficacy was 100%, the counted worms were not characterized up to the species. The applicant, therefore, proposed to restrict the claim to a single species (*D. acanthotetra)*, based on epidemiological data from the concerned area.

However, the CVMP cannot accept a species claim when no direct speciation was conducted, and speciation is only based on epidemiological data; moreover, the survey to which the applicant referred to was performed almost 10 years before the dose confirmation study and conducted in stray cats; therefore, it does not precisely reflect the population of the dose confirmation study. As a general principle, as provided by VICH GL 7, a species claim is recommended at least for adult stages.

Therefore a genus claim i.e. for *Diplopylidium spp*., cannot be accepted either, based on a single study where the finding was not in relation to the study objectives and in a case where species identification is practicable.

A claim towards *Diplopylidium* can therefore not be accepted.

2.3. Efficacy data regarding the nematode Troglostrongylus brevior

Troglostrongylus brevior belongs to the Metastrongyloidae (lungworms), like the cat lungworm *Aelurostrongylus abstrusus.* Its lifecycle involves terrestrial molluscs and a variety of cat preys as paratenic hosts. As for other nematodes, the effect against *T. brevior* is due to the presence of eprinomectin in the fixed combination.

In support of the new claim, the applicant submitted a new dose confirmation study (PRD0329601); also cross-reference was made to a field study that was previously submitted and assessed (Giannelli *et al.*, 2015).

One dose confirmation study (PRD0329601), conducted in Germany in 2015 in experimentally infested animals, was submitted in support of efficacy of a single topical application of Broadline at the recommended dose of 0.12 ml/kg body weight, against induced infections with *T. brevior*. This is a GCP-compliant study, conducted in accordance with VICH GL7 and VICH GL 20. It involved three groups of 8 animals each; one group was treated at day 6 post-infestation, one at day 28 post-infestation, and the last was left untreated.

Efficacy based on worm count reduction was 100% for both treatment time points. The reduction in larval shedding in faeces was 100% in animals treated 6 days post-infestation, with measurements starting 13 days thereafter. Animals treated 28 days post-infestation continued to shed larvae for 13 days after treatment while the reduction in larval shedding was 100%, 18-21 days after treatment. The differences were statistically significant except for the first time point, i.e. 4 days post-treatment.

Efficacy is obviously very high; however, it is not precisely known which larval stage is targeted at day 6 post-infestation. Based on the comparison with the lifecycle of the related *A. abstrusus,* and on the likely greater resemblance to adults (which would constitute a best case in regard to efficacy), it may be considered that the L4 stage was targeted.

Efficacy in field conditions against *T. brevior* was already evaluated in a field study submitted previously (Giannelli *et al.*, 2015), in the context of a type II variation for the addition of the claim for *Aelurostrongylus abstrusus*, which has subsequently been approved. In that study, 191 client-owned cats from Italy were screened for lungworm infestations through faecal examination; twenty-three individuals were positive for L1 of *A. abstrusus* (n = 18) or *T. brevior* (n = 3) or for both species (n = 2) and they were topically treated with Broadline, as a single administration. Based on lungworm larvae counts in faeces, the efficacy of the treatment was 90.5% or 100% for *A. abstrusus* or *T. brevior*, respectively. The results of that study are indicative of field efficacy against *T. brevior*, although they cannot be considered pivotal given the very low number of cats involved (n = 5). In a context of minor use, and taking into account that an efficacy of 100% is obtained after one single administration in both the laboratory study and in the few animals treated in a field setting, a claim for *T. brevior* (adults and L4 stage) can be accepted.

2.4. Efficacy data regarding the cat liver fluke Opisthorchis felineus

The cercariae of the liver fluke *Opisthorchis felineus* develop into water snails, after which metacercariae are transmitted by fish. The species has an indirect zoonotic potential. The prevalence of cat infestations is expected to greatly differ among geographical regions and countries, being only present in cats living close to the coasts of infested rivers. *O. felineus* infestation is present in Eastern Europe, central Asia and Siberia. Opisthorchiasis is a foodborne zoonotic disease. Although there is no direct transmission from cats to humans neither through contact, nor through the faeces, cats are a reservoir of parasites and a

source of contamination for water, an important transmission pathway of this parasite to humans. The effect against this class of trematodes is due to the presence of praziquantel in the product.

Efficacy against *Opisthorchis felineus* is supported only by one dose confirmation study (PRD0320501; Germany, 2015) involving 8 treated cats and 8 untreated controls. The study was conducted in accordance with VICH GL 7 and VICH GL 20 in experimentally infested cats, meaning that only one isolate is involved in the efficacy demonstration. The cats were treated twice at a 28-days interval, starting 42 days after artificial infestation. No clear justification for this treatment timing is given. The animals in this study did not receive the minimum dose within their dose band, as all of them were treated with a commercial applicator, which is considered as an important shortcoming. The volumes administered ranged between 0.16 and 0.34 ml with a median dose of approximately 0.20 ml, while the nominal minimum and maximum dose as per label are of 0.12 and 0.36 ml.

The results of the study in terms of reduction in worm counts only showed an insufficient efficacy level of 75.5% and thus, did not exceed the acceptance threshold of 90%. Besides, this threshold was also not exceeded at all time points in regard to the reduction in faecal egg counts; faecal egg counts of treated cats were reduced by 96.4%, 75.2%, 90.6%, 95.4%, 97.3%, and 97.1% for days 6/7, 12/13, 20/21, 27/28, 34/35 and 41/42 after the first treatment, respectively. The low observed efficacy at this dose is in line with published data indicating that higher praziquantel doses may be necessary to clear trematode infestations.

Therefore, the CVMP did not accept the proposed new indication ("In the context of mixed infestations, the product can additionally reduce the level of infestation with the cat liver fluke (Opisthorchis felineus))"in the section 4.2. of the SPC, as this would reflect an efficacy level lower than the 90% acceptance threshold for helminths. Accordingly, related claims (i.e. a reference to target parasitic species in SPC section 5.1) would not be accepted, when there is no corresponding indication in 4.2.

2.5. Conclusions

The efficacy towards the new claimed helminth species was assessed taking into account that a Minor Use status was granted for those indications.

- Efficacy against adult *J. pasqualei* and *J. fuhrmanni* was demonstrated in one laboratory dose confirmation study in naturally infested animals from the United Arab Emirates. The resulting efficacy percents, based on geometric means, are 99.7% for adult *J. pasqualei* and 100% for adult *J. fuhrmanni*. This is mitigated however by the poor efficacy (69.8%) towards juvenile *Joyeuxiella* spp., as defined by the impossibility to identify worms up to the species. Indeed, complete eradication of the infestation may be prevented in cats harbouring a high proportion of immature worms, which is not uncommon in view of the worm populations observed in field cats.

  It should be taken into account that the previously established efficacy against *D. caninum*, and efficacy against two different *Joyeuxiella* species and *Diplopylidium spp.*, might be indicative of overall efficacy against dipylidiid cestodes.

  Efficacy was therefore only accepted for adult *Joyeuxiella* spp., provided that the user should be warned that the presence of a high number of immature worms may preclude complete eradication.

- The product was shown to be 100% effective against unspecified *Diplopylidium* spp. in one dose confirmation study involving naturally infested cats from Qatar. However, testing efficacy against *Diplopylidium* spp. was not initially among the study objectives, and the worms were not characterized up to the species level; this leads to a genus claim, which cannot be accepted in virtue of VICH GL 7. A claim towards *Diplopylidium* was therefore not accepted.

- Efficacy against the metastrongyloid lungworm *T. brevior* is demonstrated in one dose confirmation study, in experimentally infested animals. Efficacy was 100% in cats harbouring adult worms as well as in cats harbouring larval stages.

  Further support for efficacy in field conditions against adult *T. brevior* can be drawn from a field study, were 5 naturally infested cats were treated once with the product, and 100% efficacy based on larvae counts in faeces was obtained. Considering the "minor use status", and taking into account that an efficacy of 100% is obtained after one single administration in both the laboratory study and in the few animals treated in a field setting, a claim for *T. brevior* (adults and L4 stage) can be accepted.

- Efficacy against *Opisthorchis felineus* was investigated in one dose confirmation study involving experimentally infested cats Efficacy in terms of reduction in worm counts and reduction in faecal egg counts was below the acceptance thresholds; in addition, the dosing regimen was not in line with the recommended posology. Therefore, the CVMP did not accept the proposed new indication in regard to the cat liver fluke (*Opisthorchis felineus*).

3. Benefit-risk assessment

The following new helminth species are proposed to be added to the already authorised indications for Broadline:

- The cestodes *Joyeuxiella pasqualei* (adults), *Joyeuxiella fuhrmanni* (adults) and *Diplopylidium* spp.
- The respiratory nematode *Troglostrongylus brevior* (L3, L4 and adults),
- The trematode *Opisthorchis felineus*, the cat liver fluke.

Reduced data requirements were accepted taking into account that Minor Use status was granted for those indications.

3.1. Benefit assessment

This application proposes the broadening of the indication for Broadline, spot-on solution for use in cats. The new indications will be of benefit for the target species, as they will provide new treatment options.

Results from controlled dose confirmation studies showed the efficacy of a single dose of topically applied spot-on at the recommended dose for cats against two of the proposed cestodes (adult *Joyeuxiella pasqualei* and *Joyeuxiella fuhrmanni)*, and one respiratory nematode (*Troglostrongylus brevior)*. Although the data package supporting the efficacy was somehow limited (only one, not two, dose confirmation study per claimed parasite, no new field studies), this was accepted as the parasites had been granted MUMS status.

However, insufficient data were provided to demonstrate the benefit of Broadline against another claimed cestodes (*Diplopylidium* spp.) and the cat liver fluke (*Opisthorchis felineus*).

3.2. Risk assessment

As the product will be administered to the same target species at the same dose rate and at the same frequency as already approved for existing indications, no new risk is considered to arise in terms of user safety, target animal tolerance, potential for resistance development or for the environment.

No change to the impact on the environment is envisaged.

The benefit –risk balance remains unchanged.

3.3. Evaluation of the benefit-risk balance

The benefit-risk balance is considered as favourable for adult *Joyeuxiella pasqualei* and *J. fuhrmanni*, on condition that an additional warning is inserted in section 4.4 of the SPC in order to inform the user of the possible low overall efficacy in cats harbouring high numbers of immature worms.

The benefit-risk balance is also considered positive for adult and larval (L4) *Troglostrongylus brevior*.

However, the benefit-risk balance is considered as unfavourable for the proposed claim against *Diplopylidium* spp., and *Opisthorchis felineus*, due to insufficient data on efficacy.

4. Overall conclusions of the evaluation and recommendations

This application, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested changes are met, can be approved for some but not all of the newly proposed indications, provided that further SPC amendments are implemented in section 4.4 of the SPC and in the relevant section of the package leaflet.

The following proposed new claims have been accepted:

- Treatment of infestations with tapeworms (adult *Joyeuxiella pasqualei*, adult *Joyeuxiella fuhrmanni*),
- Treatment of infestations with feline lungworms (L4 larvae and adults of *Troglostrongylus brevior*).

However, the following proposed new claims have not sufficiently been supported by efficacy data and therefore not been accepted:

- The claim towards the L3 stage of *T. brevior*.
- Treatment of infestations with tapeworms (…*Diplopylidium* spp.)
- In the context of mixed infestations, the product can additionally reduce the level of infestation with the cat liver fluke (*Opisthorchis felineus*).

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

I and IIIB