12 March 2015
EMA/CVMP/174821/2015
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/0001)

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

Rapporteur: B. Urbain

Co-Rapporteur: C. Muňoz Madero

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, MERIAL (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Broadline.

1.2 Scope of the variation

This variation is to add the following new indications for the target species (cats):

- treatment of infestations with feline lungworms (L3, L4, immature adults and adults of *Aelurostrongylus abstrusus*);
- treatment of notoedric mange (*Notoedres cati*).

Current	**Proposed**
SPC **4.2 Indications for use, specifying the target species** … Ectoparasites - Treatment and prevention of infestations by fleas (*Ctenocephalides felis)*. Elimination of fleas within 24 hours. One treatment prevents further infestations for at least one month. - Prevention of environmental flea contamination by inhibiting the development of flea immature stages (eggs, larvae and pupae) for over a month. - The product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD). - Treatment and prevention of infestations by ticks (*Ixodes ricinus)*. Elimination of ticks within 48 hours. One treatment prevents further infestations for up to 3 weeks. Cestodes - Treatment of infestations with tapeworms (*Dipylidium caninum*, *Taenia taeniaeformis*, *Echinococcus multilocularis*). Nematodes - Treatment of infestations with gastrointestinal nematodes (L3, L4 larvae and adults of *Toxocara cati*, L4 larvae and adults of *Ancylostoma tubaeforme*, and adult forms of *Toxascaris leonina* and *Ancylostoma brazilienze*). - Treatment of infestations with vesical worms (*Capillaria plica*).	**SPC** **4.2 Indications for use, specifying the target species** … Ectoparasites - Treatment and prevention of infestations by fleas (*Ctenocephalides felis)*. Elimination of fleas within 24 hours. One treatment prevents further infestations for at least one month. - Prevention of environmental flea contamination by inhibiting the development of flea immature stages (eggs, larvae and pupae) for over a month. - The product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD). - Treatment and prevention of infestations by ticks (*Ixodes ricinus)*. Elimination of ticks within 48 hours. One treatment prevents further infestations for up to 3 weeks. - Treatment of notoedric mange (*Notoedres cati*). Cestodes - Treatment of infestations with tapeworms (*Dipylidium caninum*, *Taenia taeniaeformis*, *Echinococcus multilocularis*). Nematodes - Treatment of infestations with gastrointestinal nematodes (L3, L4 larvae and adults of *Toxocara cati*, L4 larvae and adults of *Ancylostoma tubaeforme*, and adult forms of *Toxascaris leonina* and *Ancylostoma brazilienze*). - Treatment of infestations with feline lungworm (L3, L4 larvae, immature adults and adults of

- Prevention of heartworm disease (*Dirofilaria immitis* larvae) for one month.	*Aelurostrongylus abstrusus*). - Treatment of infestations with vesical worms (*Capillaria plica*). - Prevention of heartworm disease (*Dirofilaria immitis* larvae) for one month. *Package leaflet amended accordingly.*

2. Scientific discussion

2.1. Assessment

Broadline is a combination anti-parasitic product for cats, presented as a spot on solution in applicators of 0.3 ml or 0.9 ml (for cats < 2.5 kg and from 2.5 kg to 7.5 kg, respectively). The product contains four active substances, fipronil, S-methoprene, praziquantel and eprinomectin. It is indicated for cats with, or at risk of mixed infestations by cestodes, nematodes and ectoparasites. The purpose of this variation is to add indications against infestations by the cat lungworm *Aelurostrongylus abstrusus* and by the agent of cat notoedric mange, *Notoedres cati.* As a nematode species, *A. abstrusus* is targeted essentially by eprinomectin. As a mite, *N. cati* is expected to be targeted mainly by eprinomectin although fipronil could also show some activity against that species.

New indication against *Aelurostrongylus abstrusus*

The proposed claim wording in section 4.2 of the summary of product characteristics (SPC) is "Treatment of infestations with feline lungworm (L3, L4 larvae, immature adults and adults of *Aelurostrongylus abstrusus*)".

Dose confirmation studies

The first dose confirmation study was to assess the efficacy of a topically administered combination of a non-final formulation against induced infestation of *Aelurostrongylus abstrusus* in cats. This study was first provided in the original marketing authorisation (MA) application for Broadline, as the sole study supporting a claim for lungworms in cats. It was deemed insufficient by the CVMP to grant the claim against *A. abstrusus.* It is re-submitted for information and completeness but is considered by the CVMP as non-pivotal.

Twenty-four cats were enrolled in the study. The study design consisted of three equal groups of 8 experimentally infested cats, one untreated group and two treated groups receiving either one single treatment or two treatments at a 28–day interval. Infestation was induced by *A. abstrusus* on days –52, –51, –50 and –49, each inoculation with 125 L3 larvae. The results were based on L1 larval counts in faeces at days 7, 14, 21, 28, 35, 42, 49, 56 post-treatment and worm counts (in lung digesta) at day 56, as compared to controls. All control cats were positive, with a geometric mean of 34.

Figures for efficacy based on faecal larval (L1) counts in both groups after one single treatment were low (< 90%) at days 35, 42 and 49 in group 2 (one treatment) and at days 28 and 35 in group 3 (two treatments). In contrast, after the second treatment administration in group 3, efficacy remained > 99% up to the end of follow-up (day 56). According to the applicant, the location of *A. abstrusus* implies that elimination of the parasite bodies takes a long time. Lungworm burdens were reduced by only 24% and 75%, in groups 2 and 3 respectively.

The second study was conducted in accordance with the VICH GL7 on efficacy requirements for anthelmintics: overall guidelines (CVMP/VICH/832/99) and VICH GL20 on efficacy of anthelmintics: specific recommendations for felines (CVMP/VICH/545/00); and the World Association for the

Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al., 1994).

Fourty-eight cats (24 male, 24 female) aged approximately 7 to 14 months with confirmed *Aelurostrongylus* larval shedding negative by faecal examinations (day –5) were enrolled in the study. Cats were experimentally infested with *A. abstrusus* L3 larvae. The *A. abstrusus* strain used for induced infestation was isolated in 2008 from a naturally infected cat in Albania. The cats were treated with the market formulation administered according to body weight. The cats were randomized to 6 treatment groups of 8 cats each at 4, 7, 14, 32 or 4 and 32 days post- infestation, in order to target the different parasite life stages. The efficacy endpoint was the reduction of L1 larvae detected in the faeces. Faecal samples were collected from all cats on day 32, and weekly thereafter until day 60 and examined for *Aelurostrongylus* L1 larvae using the Baermann-Wetzel method.

It was concluded that the results of this experimental infestation study confirm efficacy of a single topical treatment with the candidate product against immature and adult stages of *A. abstrusus* in cats, based on the reduction of larvae release at a level of ≥ 91.6%.

The CVMP considered that this study shows adequate efficacy, when based on the acceptance threshold of 90% commonly used and recommended for direct parasite counts in situ.

The third study submitted is a good clinical practice (GCP) study conducted in Germany in accordance with the VICH GL7 and VICH GL20, and the WAAVP guidelines for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al., 1994).

Thirty-two cats were enrolled in the study. The cats were approximately 6 to 7 months. The cats were randomized to four treatment groups of 8 cats each. All four groups of cats were experimentally inoculated, group 1 were left untreated and the other three groups were treated twice at a 4–week interval, at different time points during the course of infestation. Efficacy assessment was based on L1 larval counts in faeces.

The CVMP considers that the calculated efficacy percentages in treated animals, based on faecal larval counts, and including results obtained between two administrations, which are from 97.5% to 100% up to 91 dpi (days post-inoculation), indicate a priori adequate efficacy. However, data collected at days 35 and 42 dpi, which is before any treatment in group 4, revealed an 88% to 96% reduction in counts in that group. An alternative data analysis was performed by the applicant, using baseline counts in the same group as a reference to calculate efficacy percentages. In the answers to questions it was further clarified that even if those baseline counts in group 4 (and possibly, in other treatment groups) were low relative to controls, they can still be considered as indicative of a sufficient infestation level and this, in comparison with the first study and literature studies, using naturally infested animals. Also there is no recommended threshold for acceptable infestation level.

In conclusion, the CVMP can accept that, even if those were low relative to controls, pre-treatment worm counts in group 4 (and possibly, in other treatment groups) can still be considered as indicative of a sufficient infestation and this, in comparison with other studies including literature studies with naturally infested animals, and in the absence of a recommended threshold. Therefore this study can be considered as a valid dose confirmation study to be taken into account in the overall efficacy assessment for the claim as to *Aelurostrongylus abstrusus*.

The applicant agreed to delete the term "immature" in the proposed claim for lungworms.

Due to its small size and deep location within the lung parenchyma (in the terminal bronchioles, alveolar ducts and alveoli), *A. abstrusus* cannot be rapidly eliminated after killing, and moreover, cannot be recovered without peptic digestion of the lung tissues, which damages the worms and renders impossible the distinction between live and dead worms, and likely induces a high variability in counts. The CVMP

agreed that, in view of the technical difficulties linked to worm recovery and comparison of worm burdens between treated and control animals, and of the absence of recognised method for efficacy assessment through worm counting, or of other quantitative efficacy assessment method, it was a reasonable choice to use the method based on faecal larval output.

Field study

The applicant provided a report on a limited (21 cats), uncontrolled field study investigating efficacy against *A. abstrusus* in naturally infested cats. The field study supporting the *A. abstrusus* indication was conducted in three geographical regions of Italy where the occurrence of feline lungworm infestations has been previously reported. It is not GCP. Twenty (20) owned cats were recruited and completed the follow-up. The cats were enrolled based on the detection of L1 larvae in faeces, and treated once with the product.

Seven cats showed respiratory clinical signs (dyspnoea, recurrent cough, nasal discharge, wheezing) at inclusion. At day 28(±2) post-treatment, a second faecal examination was performed. The efficacy percent was calculated based on geometric mean counts before treatment and 28 days after. The difference between pre- and post-treatment counts was statistically significant; the overall efficacy percent based on geometric mean counts was 90.5%. Efficacy percentage of more than 90% was obtained in 15 of 20 individual animals, although in 4 of them, the baseline count was only 1 or 2 LPG. Among the 5 cats with lower efficacy, baseline counts tended to be higher. One multi-infested kitten had outlying results in that the baseline of 100 LPG increased to 800 LPG post-treatment. All 7 cats presenting respiratory alterations were clinically cured at the day 28 examination, including three cats presenting less than 90% L1 shedding reduction, among which, the aforementioned kitten with an important rise in L1 larval counts. Therefore no clear correlation can be established between the anthelmintic effect and the clinical outcome.

The CVMP considered that the study has a number of deficiencies; however, overall the product was > 90% effective in reducing L1 larvae shedding after a single administration. In addition, by the end of the 28 day study period, all symptomatic animals appeared clinically cured. The CVMP concludes that in view of the overall efficacy of 90.5% in field cases and of the acceptable results obtained previously in experimental dose confirmation studies, the claim for *A. abstrusus* is sufficiently supported and can be approved.

Based on statistical analysis of the results of dose confirmation studies, revealing for the fourth-stage larvae and immature adult stage, that the two-dose regimen gave significantly higher percent efficacy than the one-dose regimen, a second treatment at a one-month interval is recommended. This remains in line with the results of the field study, where low efficacy percentage tend to be obtained in the most heavily infested animals. CVMP recommended the addition of the following wording in section 4.9 of the SPC:

"For treatment against *Aelurostrongylus abstrusus*, a second administration one month after the initial treatment may be recommended."

New indication against notoedric mange

The proposed wording for this claim in section 4.2 of the SPC is: "Treatment of notoedric mange (*Notoedres cati*)".

Notoedric mange (feline scabies) is a highly contagious skin disease of cats, caused by *Notoedres cati.* This mite resembles *Sarcoptes scabiei* in morphology and life cycle. It is an obligate parasite, transmitted by direct contact. It burrows into the epidermis and may invade hair follicles and sebaceous glands. It induces extensive alopecia, erythema, scaling and crusts, pruritus, with possible bacterial infection; the skin lesions typically involve the ears, face and neck. The disease has a zoonotic potential.

The applicant considers this claim in the context of minor use. Indeed, although notoedric mange (feline scabies) is a highly contagious disease of cats, it is of uncommon occurrence in most European countries. It may however be endemic with focal distribution in some regions of Eastern and Southern Europe such as Italy, Switzerland, Spain, Slovenia, Croatia, Poland, and Hungary. Based on this limited epidemiological prevalence, this indication is qualified as minor, and a reduced dataset was deemed relevant.

The applicant submitted a laboratory dose confirmation study to assess the efficacy of the product against natural infestations with *Notoedres cati* in cats. This GCP study was conducted in accordance with the general requirements provided in EMA guideline 7AE17a. There is no official European guidance specific for *N. cati*. The clinical, laboratory dose confirmation study was randomised and blinded.

Eighteen naturally infested cats were included in the study. Infestation by *Notoedres cati* was clinically apparent and confirmed by pre-treatment mite counts on skin scrapings. The study was carried out in two phases approximately 6–months apart. The two phases involved 10 and 8 cats, respectively. In each phase, randomisation in blocks of 2 cats was performed, so that overall the cats were randomised to an untreated control group or a treated group. The treated cats were dosed with the market formulation as per label according to body weight.

Results of the study indicate that all control cats (9 of 9) were positive at mite counts up to day 28 post-treatment. Seven out of 9 were positive at day 42, and 6 of 8 at day 56. Indeed, after day 42 one control cat was removed from the study, on welfare grounds due to progression of notoedric mange (severe dermatitis, apathy and anorexia). The geometric mean mite count in the control group ranged from 9.3 to 22.4 over the post-treatment period. No comparison of the baseline counts between groups was presented; however as calculated by the CVMP, the geometric mean count prior to treatment is 22.8 in controls and 18.9 in the treated group. All control and treated cats had clinical scores of 2 or 3 (mild or moderate skin lesions) prior to treatment.

Efficacy was calculated as the reduction in mite counts on skin scrapings, with regard to controls; counts were performed at days 14, 28, 42 and 56 post-treatment. A statistically significant reduction in mite counts was obtained, with ≥ 98.1% efficacy at all-time points. This can be considered as demonstrating efficacy according to EMA guideline 7AE17A, which requests approximately 100% for *Sarcoptes scabiei* and, if possible, more than 90% for other mange mites. Furthermore, the recorded clinical cure rate in treated animals was 78% at day 14 and then 100% up to day 56, while remaining 0% in controls; at that time 8 of 9 treated cats had healthy skin and the remaining one had healing lesions.

The CVMP considers that the provided dose confirmation study in naturally infested cats is sufficient in view of the compelling results for both mite counts and clinical assessment, and in line with previous CVMP decisions. Although there has been no formal request for a minor-use-minor-species (MUMS) classification, the indication is considered as rare so that deviation from standard requirements is acceptable.

Concerning target animal safety, as the outcome of a severe notoedric mange mite infestation may be

lethal and as the infestation is often complicated by secondary bacterial infections, CVMP recommended the following sentence to be added in section 4.4 of the SPC: "In certain individual cats *Notoedres cati* infestation may be severe or complicated by bacterial infections. In these severe cases concomitant treatment may be necessary."

Updated environmental impact assessment

Broadline spot-on for cats is intended for treatment of cats only. According to the Phase I decision tree of the VICH GL6 on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I and the CVMP supportive guideline on revised guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), veterinary medicines for treatment of non-food (companion) animals are exempt from further environmental impact assessment.

In addition, the administration of Broadline is to be based on an individual prescription basis, taking into account the parasitological status and risk, for a given animal. Accordingly, introduction of this product into the environment will be insignificant.

No increase or change of exposure is expected as a result of the proposed new indications. No further environmental impact assessment of Broadline spot-on for cats is warranted for these claims.

Product containers and any residual contents should be disposed of safely in compliance with local regulations. No further assessment or mitigation measures are deemed necessary.

No significant change in environmental exposure is expected from the new claimed indications. No further environmental risk assessment is needed.

2.2. Summary and conclusions

Indication for the treatment of *Aelurostrongylus abstrusus* infestations in cats

For the indication against *Aelurostrongylus abstrusus,* the present application comprises two valid dose confirmation studies showing > 90% reduction in L1 shedding at all-time points. These used experimental inoculation with two different field strains of *A. abstrusus*. A total of 64 treated cats, distributed in groups of 8 treated at various post-treatment time points in order to target the different parasitic stages, were involved in those two studies. Efficacy assessment was performed weekly for 4 to 9 weeks. The insufficient efficacy results from worm counts in the laboratory study submitted previously are considered adequately justified. That study also showed some insufficient larval count reductions in the course of follow-up, which can be explained among others by the high level of infestation obtained; however adequate efficacy is obtained at the end of follow-up. Furthermore, a field study involving 20 owned, naturally infested cats, shows that the product is > 90% effective in reducing L1 larvae shedding after a single administration. Taken individually, 15 of 20 animals show > 90% efficacy. All symptomatic animals appeared clinically cured, although it is impossible to formally attribute clinical efficacy to the anthelmintic effect. When considering only the cats with comparable baseline levels, the recorded anthelminthic efficacy is comparable to that obtained in literature studies using three other anthelmintics, one of which is authorised for the claimed indication. Therefore, overall it can be considered that the claimed indication against *A. abstrusus* is sufficiently demonstrated. The following wording is to be added to section 4.2 of the SPC:

"Treatment of infestations with feline lungworm (L3 larvae, L4 larvae and adults of *Aelurostrongylus abstrusus*)."

The proposed recommendation for a second treatment at a 28–day interval is considered justified in view of the results obtained in both experimentally and naturally infested animals. The following wording is to

be added to section 4.9 of the SPC:

"For treatment against *Aelurostrongylus abstrusus*, a second administration one month after the initial treatment may be recommended."

Indication for the treatment of notoedric mange (*Notoedres cati*) in cats

The mite *Notoedres cati* is an obligate parasite from the family *Sarcoptidae*. The disease is considered as rare in most Western Europe countries, and tends to occur in local outbreaks. The parasite is readily transmitted by direct contact and occurs mainly in neglected cats. The clinical manifestation is characterised by intense pruritus, hyperkeratosis and scalings, especially on the face, ears, neck and forelimbs. The symptoms may be aggravated by bacterial infections and secondary lesions due to pruritus. *N. cati* infestations have been described in dogs and other animals. It may exceptionally involve humans. It is highly contagious and its clinical manifestations can be severe. Other animals and humans may exceptionally be infected by *N. cati*.

In support of the newly proposed claim, the applicant provides one single laboratory dose confirmation study, involving naturally infected cats. This could be accepted on principle considering that the claim refers to a minor use, and that the involved animals were naturally infested.

Although at least two dose confirmation trials and field trials should be conducted according to EMA guideline 7AE17a, the principle of conducting only one laboratory study to demonstrate efficacy in cat notoedric mange, can be endorsed by the CVMP, since (i) the condition can be considered as rare and corresponding to a minor use, (ii) the disease may severely affect susceptible cats and has a zoonotic potential, and (iii) the study provided uses natural infestations.

A warning should be included in the SPC stating that the ectoparasiticide might not prevent a serious lethal outcome of a very severe notoedric mite infestation, e.g., where the symptoms are aggravated by secondary bacterial infections. Therefore, the present variation should also include the following sentence in section 4.4 of the SPC:

"In certain individual cats *Notoedres cati* infestation may be severe or complicated by bacterial infections. In these severe cases concomitant treatment may be necessary."

In conclusion for the *Notoedres cati* claim, the provided dose confirmation study in naturally infested cats is considered sufficient in a context of minor use, in view of the compelling results for both mite count reductions in regard to untreated controls, and assessment of the clinical success rate.

3. Benefit-risk assessment

3.1. Benefit assessment

The product has shown over 90% efficacy in the reduction of faecal L1 output, for a 4 to 9 week follow-up period, in two dose confirmation studies using experimental infestation by *Aelurostrongylus abstrusus* in cats. Several parasitic stages were targeted (L3, L4 larvae, adults). As efficacy is higher with a second treatment at a 28–day interval, this is recommended as the treatment regimen. A field study in 20 owned, naturally infested animals, shows that the product is overall > 90% effective in reducing L1 larvae shedding, and is > 90% effective in 15 of 20 animals taken individually. Lower efficacy tends to be observed in cats with the most heavy baseline infestation level, which also supports the recommendation for a second treatment. All symptomatic animals appeared clinically cured although no correlation seem to appear between the clinical efficacy and the anthelmintic effect. When considering the cats with comparable baseline levels the results are comparable to those obtained in literature field studies using

other authorised anthelmintics.

Over 90% efficacy in mite counts reduction, over a 56 day follow-up period, has been demonstrated in cats naturally infested by *Notoedres cati*, in one study conducted in laboratory conditions. Furthermore, in the same study a 100% clinical success rate was achieved. In a context of minor use, this is considered as adequately demonstrating efficacy of the product against *N. cati* infestations.

3.2. Risk assessment

The product has previously been shown to be well tolerated when administered as recommended, and to imply an acceptable risk as regards resistance development, on condition that an adequate SPC wording was adopted.

In both the laboratory and field studies submitted in the framework of this application, no adverse event was recorded. Also no new resistance issue can be identified in relation to the new claims which would impact the overall risk assessment for the product.

However it is considered appropriate in regard of target animal safety, to warn the user that severe notoedric mange could require concomitant treatment; the following warning should therefore be included in section 4.4 of the SPC:

"In certain individual cats *Notoedres cati* infestation may be severe or complicated by bacterial infections. In these severe cases concomitant treatment may be necessary."

No changes to user safety or environmental safety are afforded by this variation.

3.3. Evaluation of the benefit-risk balance

The CVMP considers as favourable the overall benefit-risk balance resulting from the proposed claim for *Notoedres cati* and the relating changes in the recommendations for use.

For the indication against *A. abstrusus* infestations the benefit-risk balance is also considered favourable, with a recommendation for a second treatment at a 28–days interval.

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.

The CVMP recommends updating the SPC and appropriate parts of the product information as it is described in section 2.2.

It is also recommended to restart the periodic safety update report (PSUR) cycle for Broadline to ensure more frequent pharmacovigilance monitoring due to the new indications. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 30 June 2015.

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes I and IIIB to the Community marketing authorisation.