EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for BROADLINE (EMEA/V/C/002700/II/0024)

INN: fipronil / (s)-methoprene / eprinomectin / praziquantel

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

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1. Introduction

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) on 3 May 2019 an application for a type II variation for BROADLINE.

1.2. 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

to add a new therapeutic indication: treatment of infections with *Ancylostoma ceylanicum* (L4 larvae and adults).

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed in July 2018 that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) would be applied when assessing the application. MUMS/limited market status was granted as the treatment of infections with *Ancylostoma ceylanicum* (L4 larvae and adults) in cats is considered a minor use.

2. Scientific Overview

BROADLINE is a fixed combination of four antiparasitic active substances: fipronil, (S)-methoprene, eprinomectin and praziquantel. It is a spot-on solution indicated in cats with, or at risk from mixed infestations by cestodes, nematodes and ectoparasites, as listed in the approved product information. The veterinary medicinal product is exclusively indicated when all three parasite groups are targeted at the same time.

The product is presented in topical applicators delivering 0.3 or 0.9 ml of solution, intended for cats under 2.5 kg bodyweight or cats from 2.5 to 7.5 kg bodyweight, respectively. The recommended minimum doses are 10 mg/kg bodyweight for fipronil, 12 mg/kg for (S)-methoprene, 0.5 mg/kg for eprinomectin and 10 mg/kg for praziquantel. The rationale for prescription should be tailored to the individual needs of the cat, based on the parasite species detected, the clinical assessment, the animal's lifestyle and the local epidemiological situation.

The present variation is to add a new therapeutic indication, for the treatment of infections with

Ancylostoma ceylanicum (L4 larvae and adults).

The hookworm *Ancylostoma ceylanicum* causes infections of the small intestine in dogs, cats and wild canids, which may induce gastro-intestinal signs and anaemia. The nematode is common in South-Eastern Asia, the West Pacific and some areas of Australia; it has also been observed in some regions of South America, the Middle East and Africa. It is a zoonotic pathogen which causes patent, symptomatic infections in humans; the human transmission of *A. ceylanicum* is increasingly recognised as a significant public health problem in the concerned regions. Autochthonous animal or human cases of infection with *A. ceylanicum* have not been described so far in Europe. However, there is a significant risk of infection in traveling animals; furthermore, in the future the epidemiology of the parasite might possibly evolve to European territories due to human movement and climate changes, which is all the more possible given that the life cycle of *A. ceylanicum* is direct.

Based on the current absence of *A. ceylanicum* infections in Europe, the CVMP granted a MUMS/limited market status in relation to the claimed indication.

The proposed claim is supported by one laboratory dose confirmation study in experimentally infected cats, which was conducted in Germany. The study is GCP-compliant, and has been conducted in general compliance with the relevant VICH guidelines (VICH GL 7 "Efficacy Requirements for Anthelmintics: Overall Guidelines", and VICH GL20 "Efficacy of Anthelmintics: Specific Recommendations for Felines").

Twenty-four cats (12 males and 12 females), 22-27 weeks old, confirmed negative for hookworm eggs, were inoculated orally with approx. 300 infective (L3) stages of *A. ceylanicum.* The larvae originated from a field isolate obtained in Thailand, which was approximately 2 years old. The animals were randomized to three groups of 8 cats each. The first group remained untreated, while the second and third groups were treated once topically with the final commercial product formulation, at the minimum recommended dose, on an individual body weight basis. Specifically, the second group was treated on day 4 post-infection, *i.e.* at a time point where larvae were expected to be at the L4 stage, based on the known parasite life cycle, whereas the third group was treated on day 25 post-infection in order to target an adult, patent infection. On days 22 and 35 post-infection, egg counts in faeces were performed; eggs were recovered in all untreated animals, and all treated animals were negative, i.e. showed 100% efficacy. On day 35, the animals were necropsied and worm counts were performed as well. The geometric mean count in control cats was 20.1, with a range of 8 to 35; all control animals were found to be infected. All treated animals were negative, so that the efficacy based on worm counts was 100% for both L4 and adults *A. ceylanicum.* The differences in mean counts between control and treated animals were statistically significant ($p<0.001$).

In this study, the combination product appeared safe since no adverse effects or other health problems were recorded following the treatment.

The efficacy claims against L4 and adult *A. ceylanicum* are based on a single dose confirmation study. The lack of field data and of a second laboratory dose confirmation study is considered adequately justified by the minor use status (and the reduced requirements as outlined in the "Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market", EMA/CVMP/EWP/117899/2004–Rev.1), the fact that the product is already approved for the treatment of two hookworms of the same genus, *i.e. Ancylostoma tubaeformae* and *Ancylostoma braziliense*, and the efficacy of 100% observed against both L4 and adult worms.

The CVMP therefore concludes that the efficacy for the treatment of *A. ceylanicum* (L4 and adults) is sufficiently demonstrated and the variation can be accepted.

3. Benefit-risk assessment of the proposed change

BROADLINE is authorised in cats with, or at risk from mixed infestations by cestodes, nematodes and ectoparasites; the product is exclusively indicated when all three groups are targeted at the same time. The active substances are fipronil (an insecticide and acaricide), (S)-methoprene (an insect growth regulator), eprinomectin (a macrocyclic lactone active against nematodes) and praziquantel (a synthetic isoquinoline-pyrazine derivative with activity against tapeworms). BROADLINE is presented as spot-on solution available in applicators containing 0.3 ml or 0.9 ml of product.

The proposed variation is to add a new therapeutic indication: treatment of infections with *Ancylostoma ceylanicum* (L4 larvae and adults).

The indication has been classified as MUMS/limited market and therefore reduced data requirements apply and have been considered in the assessment.

3.1. Benefit assessment

The product has shown adequate efficacy (in accordance with the applicable VICH guidelines) for the treatment of *A. ceylanicum* infections (adults and L4). This is considered as a significant benefit as this prevents the occurrence of anaemia and gastro-intestinal disorders in the cat and, importantly, reduces the risk of zoonotic transmission to humans, where the hookworm is able to establish symptomatic, patent and potentially severe infections. Although the parasite has not been reported in continental Europe to date, it is widespread in South-Eastern Asia and the Pacific and can be found in traveling humans or animals; also, the potential for future spread in Europe is acknowledged.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

This is a variation to introduce an additional indication to an existing product, and the safety profile already established at the time of initial approval, and subsequently refined through pharmacovigilance, should not be impacted by the new indication since the recommended dose rate and other conditions of use remain the same. This is in line with the experimental infection study in cats, provided in the context of the variation, and where no adverse events were observed after the treatment.

No new risk is considered to arise in terms of user safety, target animal tolerance, environmental safety or potential for resistance development.

3.3. Risk management or mitigation measures

Appropriate information is already included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

No additional risk management or mitigation measures are considered necessary.

3.4. Evaluation of the benefit-risk balance

The inclusion of an additional indication for the treatment of infections caused by *A. ceylanicum* (L4 and adults) is considered to be beneficial, without increasing the risk linked to product use.

No change to the impact of the product is envisaged on the following aspects: quality, user safety, environmental safety or target animal safety.

The benefit-risk balance remains positive.

4. Conclusion

Based on the original data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for BROADLINE can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication: treatment of infections with *Ancylostoma ceylanicum* (L4 larvae and adults).

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of this variation, section 4.2 of the SPC is updated. The corresponding section of the package leaflet is updated accordingly.