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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Stronghold Plus (EMEA/V/C/004194, EMA/VRA/0000243880)

INN: Selamectin / Sarolaner

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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Zoetis Belgium (the applicant), submitted to the European Medicines Agency (the Agency) on 23 December 2024 an application for a variation requiring assessment for Stronghold Plus.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one

The variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

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, Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Stronghold Plus is currently authorised for use in cats with, or at risk from, mixed parasitic infestations by ticks and fleas, lice, mites, gastrointestinal nematodes or heartworm. The veterinary medicinal product is exclusively indicated when used against ticks and one or more of the other target parasites is indicated at the same time. The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

Stronghold Plus is a fixed-combination product containing the active substances sarolaner and selamectin and is presented as a spot-on solution with three different pipette sizes available. The recommended minimum treatment dose is 1 mg sarolaner and 6 mg selamectin per kg bodyweight, to be administered topically. The currently authorised dose rate is also proposed for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis*.

Dipylidiasis is caused by the heteroxenous cestode *Dipylidium caninum* through ingestion of the intermediate host (fleas) by the definitive host (carnivores). *D. caninum* is also a zoonotic pathogen, although human infections are rare. Children seem the most vulnerable due to their playing habits and close proximity to pets.

To support the proposed change, two laboratory dose confirmation studies were conducted. These studies were conducted outside the European Union (USA and South Africa respectively) using the commercial formulation of Revolution Plus, in accordance with VICH GCP standards. While not performed within the EU, the studies were largely designed taking into account the relevant CVMP and VICH guidelines for efficacy of ectoparasiticides, anthelmintics, and data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats. The applicant has confirmed that Revolution Plus (US brand name) and Stronghold Plus can be considered identical with regards to formulation.

Regarding compliance of the conducted laboratory studies with Directive 2010/63/EU, the use of individual housing was accepted based on the need to prevent cross-infection between cats. In both studies, each cat was provided with appropriate enrichment items and, while physical contact was not possible, there was visual and auditory stimuli from other cats. However, no information on cage dimensions were available in the study reports.

The first laboratory dose confirmation study was conducted in the US, using US strains of *C. felis* and *D. caninum*. The study was performed in accordance with the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) and the requirements provided in the VICH GL20 Efficacy of anthelmintics: specific recommendations for felines (EMA/CVMP/VICH/545/2000).

Twenty cats were included in this study, with a range of ages and bodyweights included in the population. Prior to treatment, test animals were confirmed to be *D. caninum* negative based on PCR analysis of faecal samples collected at Day -9. All cats included in the study were also assessed for the ability to carry an adequate burden of *C. felis*, with a trial infestation with uninfected, viable adult fleas being carried out on Day -21 followed by counting and removal on Day -20. The primary efficacy variable was *D. caninum* scolex counts at necropsy (performed on Day 58). The secondary efficacy variable was the flea count conducted on each animal on study day 33 (72 ±2 hours post-infestation on Day 30).

Cats were allocated, based on pre-treatment flea counts to either the placebo control group (T01, n=10) or the Stronghold Plus-treated group (T02, n=10) which received the minimum dosage of 1 mg/kg sarolaner, and 6 mg/kg selamectin. Treatments for both groups were administered topically once on Day 0. Cats were assessed for general health at least once daily and clinical observations were conducted prior to treatment and at 1, 3, 6, and 24 hours after treatment.

All cats were infested with 100 (±5) adult *C. felis* (infected with *D. caninum*) after treatment on Day 0 and on Days 7, 14, 21, and 30. Flea counts (with removal) were conducted 72 hours after the last infestation, on Day 33. Flea efficacy was calculated based on the reduction of arithmetic means between the Stronghold Plus-treated group and the control group. Cats were allowed to engage in normal grooming behaviour throughout the course of study to mimic the natural infection method of *D. caninum*.

The second dose confirmation study followed an identical study design, with the only exceptions being the timing of the assessment of host suitability (trial flea infestation at Day -8 and counting and removal at Day -7) and the use of an EU-origin *D. caninum* strain.

While it is noted that the *C. felis* strains used in both dose confirmation studies were of US origin, the applicant's justification that the results obtained are also applicable to the EU can be accepted. The efficacy of Stronghold Plus against the vector *C. felis* under field conditions in the EU was assessed and accepted by CVMP during the original marketing authorisation application (MAA) for Stronghold Plus. Uniform susceptibility of *C. felis* between the EU and US was demonstrated in the original MAA of Stronghold Plus (EMA/849714/2016) in which both the dose confirmation study with an EU strain and

dose confirmation study with a non-EU strain showed very high immediate and persistent efficacy (ranging from 92.4–100%), indicating uniform susceptibility across geographies. In the pivotal safety and efficacy clinical field trial, high 14-day and 30-day efficacy results were observed (97.3% and 97.1%, respectively).

Although a US strain of *D. caninum* was used in the first dose confirmation study, no differences for EU strains are anticipated as it has been shown that the distinct genotypes of the *D. caninum* population are related to host origin (dogs or cats), irrespective of their geographical origin (Labuschagne et al. 2018). Moreover, the effect of Stronghold Plus (selamectin and sarolaner) is against the flea vector rather than the tapeworm, which renders the specific strain of *D. caninum* of lesser importance for the reduction claim sought for the VMP. The strain of *D. caninum* used in the second dose confirmation study was of EU (Greek) origin. This lends support to the anticipated efficacy for reduction of infection risk when Stronghold Plus is administered to cats in European field conditions. However, as mentioned previously, the specific strain of *D. caninum* is of lesser importance for the reduction claim sought.

Primary efficacy results, based on *D. caninum* scolex counts, showed a reduction in geometric mean counts for Stronghold Plus compared to placebo-treated animals in both dose confirmation studies. Reductions of 99.3% and 97.1 in *D. caninum* scolex counts were reported in the US and South African studies, respectively; that is, above the efficacy threshold of ≥90% recommended by the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015). Adequacy of *D. caninum* infection in accordance with VICH GL20 Efficacy of anthelmintics: specific recommendations for felines (EMA/CVMP/VICH/545/2000) was also demonstrated in both studies. 100% and 80% of control group cats in the US and South African studies, respectively, had ≥2 adult *D. caninum* scoleces at the time of necropsy, compared with 20% and 10% in the corresponding Revolution Plus-treated groups in each case.

With regards to the secondary efficacy variable, the reduction in flea counts at Day 33 compared to the placebo-treated group were 94.3% and 100% for Revolution Plus-treated groups in the US and South African studies, respectively. It is noted that the efficacy against *C. felis* reported in the US study falls slightly short (94.3%) of the expected level (95%) recommended in the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000). However, given the proximity to guideline requirements, and considering the body of original and complementary evidence provided by the applicant regarding efficacy against *C. felis*, it can be accepted that Stronghold Plus is expected to have adequate efficacy in the treatment and prevention of *C. felis* under field conditions. The non-treated control groups maintained high mean flea counts following multiple infestations, with least squares means of 56.3 and 96.2 in the US and South African studies, respectively. Adequacy of flea infestation was demonstrated on the basis that >60.0% of control animals in each study maintained ≥50 fleas following the final flea infestation on Day 30.

In relation to target animal safety, the IVP appears to have been generally well-tolerated by cats across both studies. The only adverse clinical signs observed in either study occurred prior to administration of the test article. The product information literature pertaining to safe use in the target species is therefore considered to be adequate in its current state.

It is noted that the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) stipulates that at least one laboratory study and one clinical trial is needed for each claimed vector-borne pathogen, unless otherwise justified. However, it is accepted that a high level of efficacy against *C. felis* (and consequently transmission of *D. caninum*) was

demonstrated in the presented laboratory dose confirmation studies conducted in two different locations using different flea and tapeworm strains.

Additionally, it is noted that proglottid shedding from *D. caninum* infected cats can be variable and inconsistent, and that faecal flotation significantly underestimates prevalence compared to necropsy. Given that terminal procedures are not possible under field conditions, and that results presented using other diagnostic methods often preclude accurate conclusions from being drawn, it can be accepted that the approach taken by the applicant is appropriate in the context of *D. caninum*.

The *D. caninum* infection rate (6.7 to 53.3%) in the study fleas is also much higher than the 2.2% infection rate reported in the field according to published literature. All cats were also repeatedly infested (weekly infestations for one month), and this is considered to mimic a high and prolonged infection pressure.

Furthermore, the efficacy of Stronghold Plus against fleas under field conditions in the EU has previously been assessed and accepted by the CVMP during the original MAA of Stronghold Plus. Based on the totality of evidence presented with the original and current applications, it is considered that the omission of a clinical trial has been adequately justified by the applicant.

The recommended dose rate for Stronghold Plus will remain unchanged as a result of this variation, and appropriate guidance is given in relation to reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* in the proposed SPC.

In conclusion, based on the findings of the two dose confirmation studies presented, it is accepted that Stronghold Plus, when administered to cats on a single occasion at the minimum recommended therapeutic dose, achieved an adequate level of efficacy for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment. As such, the proposed variation can be accepted.

The applicant has also taken the opportunity to align the product information with version 9.1 of the QRD template. This is considered acceptable.

3. Benefit-risk assessment of the proposed change

Stronghold Plus is currently authorised for use in cats with, or at risk from, mixed parasitic infestations by ticks and fleas, lice, mites, gastrointestinal nematodes or heartworm. The veterinary medicinal product is exclusively indicated when used against ticks and one or more of the other target parasites is indicated at the same time. The active substances are sarolaner (an acaricide and insecticide belonging to the isoxazoline family) and selamectin (a semi-synthetic compound of the avermectin class). Stronghold Plus is authorised as a spot-on solution with three different strengths and is administered at a dose of 1–2 mg/kg bodyweight of sarolaner, and 6–12 mg/kg bodyweight of selamectin.

The proposed variation concerns change(s) to therapeutic indication(s) – addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of Stronghold Plus is its efficacy in the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* in cats for one month after treatment, which was established in two GCP-compliant laboratory dose confirmation studies.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety for the user, environment, and target animal remains unaffected by this variation.

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of Stronghold Plus in accordance with SPC recommendations is generally well tolerated.

Risk for the user:

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

Stronghold Plus is not expected to pose a risk for the environment when used according to the SPC recommendations. The veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

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

3.4. Evaluation of the benefit-risk balance

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

The product has been shown to be efficacious in cats for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Stronghold Plus can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment. The product information has also been aligned with version 9.1 of the QRD template.

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, sections 3.2, 3.6 and 4.2 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.