EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 October 2015
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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP assessment report for Stronghold 360 mg for dogs and 60 mg for cats (EMEA/V/C/000050/X/0051/G)

International non-proprietary name: Selamectin

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

[1] Minor corrections in part 3.

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# Product profile

| | |
|---|---|
| Invented name: | Stronghold |
| Active substances: | Selamectin |
| Target species: | Cats and dogs |
| Pharmaceutical form: | Spot-on solution |
| Strength: | 60 mg and 360 mg |
| Therapeutic Indication: | **Cats and dogs**: treatment and prevention of flea infestations caused by *Ctenocephalides* spp. for one month following a single administration. This is as a result of the adulticidal, larvicidal and ovicidal properties of the product. The product is ovicidal for three weeks after administration. Through a reduction in the flea population, monthly treatment of pregnant and lactating animals will also aid in the prevention of flea infestations in the litter up to seven weeks of age. The product can be used as part of a treatment strategy for flea-allergy dermatitis and through its ovicidal and larvicidal action may aid in the control of existing environmental flea infestations in areas to which the animal has access.<br><br>**Cats and dogs**: prevention of heartworm disease caused by *Dirofilaria immitis* with monthly administration.<br>Stronghold may be safely administered to animals infected with adult heartworms, however, it is recommended, in accordance with good veterinary practice, that all animals six months of age or more living in countries where a vector exists should be tested for existing adult heartworm infections before beginning medication with Stronghold. It is also recommended that dogs should be tested periodically for adult heartworm infections, as an integral part of a heartworm prevention strategy, even when Stronghold has been administered monthly. This product is not effective against adult *D. immitis*.<br><br>**Cats and dogs**: treatment of ear mites (*O. cynotis*).<br><br>**Cats**: treatment of adult roundworms (*Toxocara cati*) and adult intestinal hookworms (*Ancylostoma tubaeforme*).<br><br>**Cats**: treatment of biting-lice infestations (*Felicola subrostratus*).<br><br>**Dogs**: treatment of biting-lice infestations (*Trichodectes canis*).<br><br>**Dogs**: treatment of sarcoptic mange (caused by *S. scabiei*).<br><br>**Dogs**: treatment of adult intestinal roundworms (*Toxocara canis*). |
| ATCvet code: | QP54AA05 |
| Pharmaco-therapeutic group: | Antiparasitic products, insecticides and repellents |
| Applicant: | Zoetis Belgium SA |

# Introduction

On 27 May 2014 a grouped extension application to the Community marketing authorisation for Stronghold was submitted by Zoetis Belgium SA to the European Medicines Agency (the Agency) in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

The already authorised product Stronghold, a spot-on solution for cats and dogs, was first authorised for use in the European Union (EU) on 25 November 1999. It is currently available for cats in strengths of 15 mg and 45 mg selamectin per (single-dose) pipette; and in dogs in strengths of 15 mg, 30 mg, 60 mg, 120 mg and 240 mg selamectin per (single-dose) pipette.

This extension application consists of one extension and one type II variation and is to add new strength of the spot-on solution in the single-dose pipettes, 360 mg for dogs, and secondly to add cats to existing strength of 60 mg. These new presentations will allow the use of a single pipette, instead of the contents of 2 pipettes, for larger sized dogs or cats.

The indication remains unchanged: "Cats and dogs: treatment of ear mites (*Otodectes cynotis*). Cats: treatment of adult roundworms (*Toxocara cati*) and adult intestinal hookworms (*Ancylostoma tubaeforme*); Cats: treatment of biting lice infestations (*Felicola subrostratus*); Dogs: treatment of biting lice infestations (*Trichodectes canis*); Dogs: treatment of sarcoptic mange (caused by *Sarcoptes scabiei*). Dogs: treatment of adult intestinal roundworms (*Toxocara canis*)."

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof. The rapporteur for the application is H. Jukes, and the co-rapporteur is I. Malemis.

On 15 January 2015 the CVMP adopted an opinion and CVMP assessment report.

On 11 March 2015, the European Commission adopted a Commission Decision granting the extension to the marketing authorisation for Stronghold.

# Part 1 - Administrative particulars

### *Detailed description of the pharmacovigilance system*

The applicant has provided a detailed description of the pharmacovigilance system (version 1.2 dated 18 July 2013). Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the EU or in a third country has been provided.

### *Manufacturing authorisations and inspection status*

The active substance, selamectin, is manufactured, tested and released outside the EU. A declaration of compliance with good manufacturing practice (GMP) for this manufacturing site was provided by the qualified person of the EU batch release site, and made on the basis of an audit.

Manufacturing, primary and secondary packaging of the finished product is carried out outside the EU. A certificate of GMP compliance was provided, issued by Medicines and Healthcare Products Regulatory Agency, UK, based on an inspection in 2011. Additional sites for secondary packaging are two sites for which valid certificates of GMP compliance are available.

Batch release for the EU will be carried out by Zoetis Belgium SA. A valid certificate of GMP compliance and a valid manufacturing authorisation were provided.

The following former sites of manufacturing were deleted (via a type IA variation procedure) during this extension procedure: Pfizer Ltd, Sandwich, UK; Pfizer Amboise, France and Pfizer Service Company BVBA, Zaventem, Belgium (batch release site).

All relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate. Hence, no GMP inspections were deemed necessary within the scope of this application procedure.

***Overall conclusions on administrative particulars***

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

# Part 2 - Quality

## *Composition*

Stronghold is available in two formulations of 60 mg/ml and 120 mg/ml spot-on solutions in different strengths, i.e. 15 mg, 45 mg, 30 mg, 60 mg, 120 mg and 240 mg, presented in single-dose polypropylene pipettes of various volume sizes (indicated by different colours of the pipette caps).

The current application is to add firstly a new strength of 360 mg selamectin for dogs in a pipette containing 3 ml (also a new larger size of the primary packaging) of the 120 mg/ml solution, and secondly to add a new non-food producing species (cats) to strength of 60 mg selamectin in a pipette containing 1 ml of the 60 mg/ml solution.

The excipients used in the formulations are unchanged and are dipropylene glycol methyl ether, butylated hydroxytoluene, isopropyl alcohol and nitrogen.

## *Container*

Stronghold is presented in translucent polypropylene single-dose pipettes containing various volumes which are packed (singly) in an aluminium and aluminium/polyvinylchloride (PVC) blister overwrap. At present the product is available in packs of three pipettes (all strengths), six pipettes (all strengths except 15 mg selamectin), or fifteen pipettes (15 mg selamectin only). The new 360 mg strength for dogs will be available in a 3 ml pipette (a new larger size of the primary packaging). The 60 mg strength for cats will be available in a 1 ml pipette, which is currently used for the 15 mg, 45 mg, 30 mg, 60 mg and 120 mg presentations but with different fill volumes.

Both of these strengths will be supplied in outer packages of three and six pipettes.

## *Development pharmaceutics*

This application is to add a new strength 360 mg selamectin for dogs, presented in a pipette filled with 3 ml of the 120 mg/ml formulation and to add cats to the 60 mg strength, presented in a pipette filled with 1 ml of the 60 mg/ml formulation. There is no difference in the qualitative or quantitative composition of either of the two strength solutions used to fill the pipettes.

The new presentations are currently manufactured for the US and other global markets, using a manufacturing process identical to that for the 7 presentations previously approved in the EU. The only differences between the 7 presentations currently approved in the EU and the 2 new presentations proposed are in the final fill volumes and the pipette sizes.

The 3 ml pipette (360 mg strength) and the 1 ml pipette (60 mg strength) are manufactured from the same materials as the pipettes used for the other strengths.

All existing and proposed pipette sizes are then packaged in the same cold-formed aluminium blisters.

Given these similarities, the stability of both the 60 mg and the 360 mg strength would be expected to be identical to that for the other strengths.

### *Method of manufacture*

The new presentations are currently manufactured for the US and other global markets, using a manufacturing process identical to that for the 7 presentations previously approved in the EU. The only differences between the 7 presentations currently approved in the EU and the 2 new strengths proposed are in their final fill volumes and the new larger pipette size (3 ml for the 360 mg product). The differences are in the fill volume, and in the case of the 360 mg product, the pipette size.

Given that the manufacturing process is identical to that for all the existing product presentations and that the new presentations have been manufactured commercially for over ten years in other (non-EU) countries, the lack of process validation data for these pipette sizes/fill volumes is considered acceptable.

## *Control of starting materials*

### *Active substance*

No data are provided. However, as the active substance, selamectin, is identical to that used in the current presentations of Stronghold, the omission of data is considered acceptable.

### *Excipients*

No data are provided. However, as the excipients are identical to those used in the current presentations of Stronghold, the omission of data on them is considered acceptable.

## *Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies*

A transmissible spongiform encephalopathy (TSE) declaration was not provided. However, the bulk solutions, packaging and manufacturing process are the same as for the approved presentations of Stronghold, where for the previous renewal and variation applications TSE declarations were provided.

None of the starting materials used for the active substance selamectin or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

## *Control tests on the finished product*

This part of the dossier does not refer specifically to the new 3 ml pipette for the 360 mg strength for dogs or the new 1 ml pipette for the 60 mg strength for cats. Currently, the specifications for the 60 mg/ml solution and the 120 mg/ml solution are identical. Copies are included in the dossier. The selamectin

content of the different presentations, 15 mg and 45 mg for the 60 mg/ml solution and 30 mg, 60 mg, 120 mg and 240 mg for the 120 mg/ml solution is accommodated by the test for selamectin content which is expressed in terms of percentage of label claim as mg per dose dispensed. It is considered acceptable to continue with the same specification presented in the same manner for release of the new presentations, 60 mg for the 60 mg/ml solution and 360 mg for the 120 mg/ml solution. Therefore no new documentation is required. The analytical methods and their validation are acceptable.

No batch analysis data were presented. This is acceptable due to the similarity with the existing presentations.

## *Stability*

Extensive shelf life stability data for up to 48 months are provided for the product stored at 30 °C, in support of the claimed shelf life of 3 years for the new 360 mg strength for dogs and the 60 mg strength for cats. The stability data included three batches of the 60 mg strength pipette stored at 30 °C/60% relative humidity (RH) and four batches of the new 360 mg strength pipette, one of which was stored at 30 °C /65% RH and all four of which were stored at 30 °C/60% RH.

Also included is a large volume of supporting data from the other already authorised presentations. The samples have been evaluated by monitoring appearance, colour, assay, impurities, antioxidant content, water content and mean dose volume dispensed. Based upon the other stability-indicating parameters (appearance, colour, increase in impurity content, antioxidant content and water content) the data show that for storage at 30 °C there is no difference in stability profile between the approved presentations and the new proposed 1 ml pipette (60 mg strength) for cats and the proposed new 3 ml pipette (360 mg strength) for dogs.

No additional light stability data are presented. No changes to the warnings on the summary of product characteristics (SPC) are required as a result of the adoption of the new presentations.

A shelf life of 3 years (36 months), without restriction on the temperature of storage, is therefore supported.

## *Overall conclusions on quality*

Only limited quality data were provided in support of this application but this is considered acceptable as the formulations of the two (6% and 12% w/v) solutions used to fill the pipettes for the two strengths are identical to those used for the already authorised presentations for which full data is available and has been previously assessed as satisfactory. This is acceptable, as the relevant necessary additional data have been provided for the new presentations.

The two applied strengths differ from the already authorised presentations only in their fill volumes, and in the case of the 360 mg strength also because it is a new larger size pipette.

The new presentations are currently manufactured for the US and other global markets using a manufacturing process identical to that for the presentations currently approved in the EU. Given that the manufacturing process is identical to that for the existing product and that the new presentations have been manufactured commercially for over ten years, the lack of process validation data for these pipette sizes/fill volumes is considered acceptable.

Stability data were provided for the new presentations which support the shelf life of 3 years without any specific storage conditions.

### *Recommendation for future quality development*

None.

# Part 3 – Safety

This application concerns the addition of new presentations (a 3 ml pipette/360 mg selamectin strength for dogs and 1 ml pipette/60 mg selamectin strength for cats) which provide single pipette dosing for an additional body weight range in both cats and dogs; thus eliminating the use of appropriate combination of pipettes for cats > 10 kg and dogs > 60 kg. The product formulation, indications, target species (in general), and dosing regimen have not changed.

A new study on acute dermal toxicity rats and a single-dose oral toxicity study in mice and Sprague-Dawley rats already submitted in the original dossier have been provided. These are considered in the user safety risk assessment section below.

Reference is made to the safety documentation of the initial authorisation procedure of Stronghold 15 mg, 30 mg, 45 mg, 60 mg, 120 mg and 240 mg spot-on solution. As the pharmacology and toxicology of the active substance have been addressed previously as part of the dossier for the original application, making cross-reference to the previous assessment is considered acceptable.

## *Safety documentation*

## *Toxicological studies*

**Acute dermal toxicity in the rat**

The objective of this good laboratory practice (GLP) compliant study (A391N-US-13-130) was to assess the acute dermal toxicity of selamectin at 60 mg/ml administered by the OECD (The Organisation for Economic Co-operation and Development) 402 method.

The test product was applied to the intact skin of 5 male and 5 female Sprague-Dawley rats at a dose of 2,020 mg/kg bodyweight (bw), corresponding to a selamectin dose of 142.8 mg/kg bw. Neither deaths nor clinical signs of toxicity or irritation occurred at any time throughout the study. Gross necropsy at termination revealed no observable abnormalities. The acute dermal $LD_{50}$ was determined to be greater than 2,020 mg/kg bw for the formulation, corresponding to a $LD_{50}$ of > 142.9 mg/kg bw for selamectin. This study was not considered as directly relevant for the user risk assessment.

**Single-dose oral toxicity in the CD1 mice and Sprague-Dawley rats**

In this GLP compliant study (assessed within the initial marketing authorisation procedure) at a selamectin dose of 1,600 mg/kg bw, no deaths occurred. Diarrhoea occurred in both control and treated groups; however, with higher incidence in the selamectin-treated group. In addition, a range of clinical signs were present in rats treated with 1,600 mg/kg bw and consisted of dyspnoea, hunched posture, partially closed eyes, decreased activity, chromodacryorrhoea and piloerection. Under the conditions of this study, the minimal oral lethal dose of selamectin in rats was in excess of 1,600 mg/kg bw.

At that time CVMP concluded that the low number of animals per group used in this study did not provide sufficient statistical confidence in the results. However, selamectin was clearly of low acute oral toxicity.

## *Tolerance in the target species of animal*

See Part 4.

No data were submitted. This is considered acceptable, given that dosing of cats weighing over 7.5 kg and dogs over 40 kg is already permitted in the currently authorised SPC based on a minimum dose of 6 mg/kg bw; this is presently achieved by using a combination of pipettes of different size.

Given the combinations currently available for the cat (15 mg and 45 mg), the 60 mg strength is likely to exactly duplicate the dose in milligrams administered to a 7.6–10 kg cat following the current SPC.

For dogs weighing between 40.1 and 60 kg the proposed 40.1–60 kg dose band for the new 360 mg pipette is in fact lower than for already authorised pipette strengths, so this is not considered to be a concern for target animal safety.

It can be expected that the new presentations have the same safety profile for cats and dogs as the authorised presentations.

## *User safety*

In support of this application the applicant has presented an updated user safety risk assessment (URA) which has been conducted in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03–Rev.1).

The current application is for the addition of a new and largest strength of 360 mg selamectin for dogs in a new 3.0 ml pipette, and the addition for cats of a 60 mg selamectin strength in a 1.0 ml pipette. These additional pipettes are aimed at providing single pipette dosing for larger sized dogs and cats.

The updated URA does not consider the new strength for use in cats, 60 mg selamectin, as the 60 mg strength was already assessed in the initial application of Stronghold; only the risk to the user concerning the new and largest strength of 360 mg selamectin has been addressed, in particular:

- Acute oral toxicity, to account for the risk of ingestion by a child from the new largest strength (360 mg) for use in dogs.
- Acute dermal and oral (hand-to-mouth) toxicity, to account for exposure of a child stroking a treated pet.
- Acute dermal toxicity, to account for accidental spilling of contents from new the largest strength (360 mg) on to the adult user's skin when administering to animal.

The applicant has considered all the potential routes of accidental contact with the product and concluded that as per the authorised strengths, the most likely are those of ocular, dermal and/or oral exposure which apply to the 360 mg strength, too. For the case of accidental ocular exposure a respective safety warning is included in the product information of the authorised presentations which is considered appropriate for the 360 mg strength as well.

A no observed adverse effect level (NOAEL) of 5 mg/kg bw from a 3-month oral toxicity study in rats which was part of the original application was considered suitable for use in the URA.

Regarding the risk from oral exposure to a child, the applicant has considered a 15 kg child ingesting the entire contents of an unattended open pipette of the product. The CVMP suggests that the worst-case representation of weight for a child is 10 kg. This results in an estimated exposure of 36 mg selamectin/kg bw and a MOE (margin of exposure) of 0.14. Although the MOE value is lower than 100, it may be considered to be acceptable because the NOAEL was based on a repeated dose study whereas the

accidental exposure scenario (following the ingestion of an entire pipette) is considered a single (and unlikely) exposure event. Furthermore, as the product is presented as pipettes individually packaged in an aluminium and aluminium/PVC blister overwrap, the child will be deterred from opening a pipette of the product, which, together with the warning of "Keep out of sight and reach of children", will mitigate the risk of a child opening a pipette and ingesting the contents.

Regarding the risk from the product to children from stroking treated pets, the MOE values for dermal and oral (hand-to-mouth) scenarios using the EPA (2012) SOP are 44.64 and 4464, respectively. It is noted that, in the absence of a sub-chronic dermal NOAEL or information with respect to the dermal absorption of selamectin, the applicant has used the oral NOAEL to determine the MOE for the dermal route. This is considered to be a very much worst-case approach for determining the risk from dermal exposure and therefore can be accepted. The MOE for oral exposure is considered satisfactory. However, although the use of an oral NOAEL to determine the MOE for dermal exposure is likely to be conservative, the MOE from dermal exposure following stroking of treated dogs by children is lower than 100. As the applicant has not refined the URA by conducting a 'wipe test', it is not possible to define a precise time over which contact should be avoided.

Regarding the risk from dermal exposure to an adult, the scenario of a 60 kg adult administering 10% of the contents from the largest size pipette onto themselves (36 mg selamectin) is acceptable. The resultant MOE is 8.3. Although this MOE is less than 100, it can be agreed that existing mitigation measures are in place to manage this risk, notably the packaging design and user safety warnings to "wash off any product in contact with the skin immediately with soap and water".

The CVMP is of the opinion that due to the low MOE for dermal exposure, the existing risk mitigation warnings (in the SPC) should be strengthened to read as follows:

- This product is highly flammable; keep away from heat, sparks, open flames or other sources of ignition.
- Do not smoke, eat or drink while handling the product.
- Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and seek medical advice immediately and show the package leaflet or the label to the physician.
- Avoid direct contact with treated animals until the application site is dry. On the day of treatment, children must not handle treated animals and the animals should not be permitted to sleep with their owners, especially children. Used applicators should be disposed of immediately and not left within the sight or reach of children.
- People with sensitive skin or known allergy to veterinary medicinal products of this type should handle the veterinary medicinal product with caution.

The following warning sentence pertaining to flammability has been moved to section 4.5. 'Special precautions for use in animals':

- Keep treated animals away from fires and other sources of ignition for at least 30 minutes or until the hair coat is dry.

## *Environmental risk assessment*

An environmental risk assessment (ERA) was provided in accordance with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL6 on environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL). Given that the product and the new presentations are for the treatment of companion animals (cats and dogs), the environmental risk assessment can stop at Phase I.

Stronghold is not expected to pose a risk for the environment when used according to the SPC.

The standard warning for antiparasitics in section 4.5 of the SPC "Do not allow treated animals to bathe in water courses until at least two hours after treatment administration." is equally relevant for the new presentations.

### *Overall conclusions on the safety documentation*

The current application is for the addition of a new strength of 360 mg selamectin per pipette (3 ml) for dogs weighing 40.1 to 60.0 kg, and also the addition of strength of 60 mg selamectin per pipette (1 ml) for cats weighing between 7.5 and 10.0 kg.

The product formulation, indications, target species (in general) and dosing regimen have not changed. Given that dosing of cats weighing over 7.5 kg and dogs over 40 kg is already permitted in the currently authorised SPC of Stronghold based on a minimum dose of 6 mg/kg, it is considered that the safety profile of the new presentations in the target animals is the same as for the authorised presentations.

A user safety risk assessment was provided assessing the risk for the new and largest strength of 360 mg (3 ml pipette) only which is considered acceptable as the 60 mg strength was already considered in the URA of the initial authorisation. Based on the URA, the CVMP is of the opinion that due to the low MOE for dermal exposure, the existing risk mitigation warnings should be strengthened to ensure the safety of the user, and in particular children, and this was done (see above).

Stronghold is not expected to pose a risk for the environment when used according to the SPC.

## Residues documentation

Not applicable.

## Part 4 – Efficacy

Currently, the two solutions of Stronghold 60 mg/ml and 120 mg/ml are available in a range of dose sizes for different weight groups for dogs and cats and the addition of the new presentations (underlined) is shown below:

| Bodyweight | Selamectin content | Solution concentration | Nominal volume |
|---|---|---|---|
| Cats and Dogs< 2.5 kg | 15 mg | 60 mg/ml | 0.25 ml |
| Cats 2.6-7.5 kg | 45 mg | 60 mg/ml | 0.75 ml |
| Cats 7.6-10.0 kg | 60 mg | 60 mg/ml | 1.0 ml |
| Cats >~~7.5~~ 10.0 kg | Appropriate combination of pipettes | 60 mg/ml | Appropriate combination of pipettes |
| Dogs 2.6-5.0 kg | 30 mg | 120 mg/ml | 0.25 ml |
| Dogs 5.1-10.0 kg | 60 mg | 120 mg/ml | 0.5 ml |
| Dogs 10.1-20.0 kg | 120 mg | 120 mg/ml | 1.0 ml |
| Dogs 20.1-40.0 kg | 240 mg | 120 mg/ml | 2.0 ml |
| Dogs 40.1-60.0 kg | 360 mg | 120 mg/ml | 3.0 ml |
| Dogs >~~40~~ 60.0 kg | Appropriate combination of pipettes | 60/120 mg/ml | Appropriate combination of pipettes |

**Cats:**

The current authorisation recommends the use of "an appropriate combination" of pipettes for cats weighing more than 7.5 kg bw. The new presentation would allow the use of a single pipette in larger cats (7.6–10 kg bw), avoiding the need to combine different pipette sizes to treat this weight group of cats. A combination of pipettes would then only still be necessary for cats weighing more than 10 kg bw.

The new pipette contains the same 60 mg/ml formulation (6% w/v solution) as currently authorised pipettes in cats, but in a proportionately greater quantity (1 ml). The 60 mg strength is currently authorised in dogs, although in a smaller pipette size (0.5 ml) of a higher concentration (12%). The new 1 ml pipette would be of a lower concentration (6%) but deliver the same amount of active substance per use (60 mg).

The proposed dose administered for the new 60 mg strength for cats will be within the already authorised dose range (approximately 6–17 mg/kg bw), and the treatment of cats weighing over 7.5 kg was already authorised on the basis of the previously assessed safety and efficacy data.

**Dogs:**

The current authorisation recommends the use of "an appropriate combination" of pipettes (6% or 12%) for dogs weighing more than 40 kg bw. The new strength (360 mg) would allow the use of a single pipette in larger (40.1–60 kg bw) dogs, avoiding the need to combine different pipette sizes for this group of animals. A combination of pipettes would then only still be necessary for dogs weighing more than 60 kg bw.

The new strength contains the same 120 mg/ml formulation (12% w/v solution) as all but one of the currently authorised dog pipettes, but in a proportionately greater quantity (3 ml).

The proposed dose administered for the new 360 mg strength for dogs will be within the already authorised dose range (approximately 6–12 mg/kg bw), and the treatment of dogs weighing over 40 kg was already authorised on the basis of the previously assessed safety and efficacy data.

The 60 mg/ml and 120 mg/ml formulations are identical to those already authorised. Dosing of cats weighing over 7.5 kg and dogs over 40 kg is already permitted in the currently authorised SPC based on a minimum dose of 6 mg/kg; this is currently achieved by using a combination of pipette sizes. Given the combinations currently available for the cat (15 mg and 45 mg), the addition of the 60 mg strength is likely to exactly duplicate the dose in milligrams administered to a 7.6–10 kg cat following the current SPC.

This is not necessarily the case for dogs: dogs weighing between 40.1 kg and 60 kg are likely to be treated more accurately when the dose is calculated using a combination of pipettes than with a single 360 mg pipette (for example, using the current SPC a 50 kg dog would be treated with a 60 mg and a 240 mg pipette, giving a total dose of 300 mg [or 6 mg/kg]). However, it is acknowledged that the maximum mg/kg dose for the proposed 40.1–60 kg dose band for the new 360 mg pipette is in fact lower than for already authorised pipette strengths, so this is not considered to be a concern for target animal safety.

## *Overall conclusions on efficacy*

On the strength of the target animal safety and efficacy data previously assessed, the addition of these presentations including larger size pipettes is considered acceptable without the need for any supplementary data. The respective amendments to the SPC are satisfactory.

# Part 5 – Benefit-risk assessment

## *Introduction*

Stronghold is a spot-on solution for cats and dogs for the treatment and prevention of diseases caused by endo- and ecto-parasites. The product contains the active substance selamectin, which is a semi-synthetic compound of the avermectin class. Currently, larger sized animals (dogs above 40 kg bw and cats above 7.5 kg bw) are to be treated with a combination of the existing presentations of Stronghold.

This application is firstly to add a new strength of 360 mg in a 3 ml pipette (new larger pipette) for dogs, and secondly for cats to add an already existing strength (60 mg) although in a different pipette size (1 ml) to that already authorised for dogs (0.5 ml). These new presentations will allow animal owners to use single pipettes for larger sized dogs (40.1–60 kg bw) and for larger sized cats (7.6–10 kg bw). Therefore only dogs heavier than 60 kg and cats heavier than 10 kg bw would still need to be treated with a combination of pipette sizes.

Throughout the dossier cross-reference has been made to data already submitted and assessed in previous applications, except for data that are specific for these presentations.

## *Benefit assessment*

## Direct therapeutic benefit

Stronghold contains selamectin as active substance, an antiparasitic and anthelminthic substance of the family of avermectins. It acts as agonist of the GABA (gamma-aminobutyric acid) neurotransmitter in nerve cells and also binds to glutamate-gated chloride channels in nerve and muscle cells of invertebrates. In both cases it blocks the transmission of neuronal signals of the parasites, which are either paralysed and expelled out of the body or they starve. It also affects the reproduction of some parasites by diminishing oviposition or inducing an abnormal oogenesis.

The product is for spot-on use on cats and on dogs for the treatment and prevention of diseases caused by endo- and ecto-parasites. It is available in different strengths for animals of different weight groups.

Stronghold has been shown to be effective for the following indication: Cats and dogs: treatment of ear mites (*Otodectes cynotis*); Cats: treatment of adult roundworms (*Toxocara cati*) and adult intestinal hookworms (*Ancylostoma tubaeforme*); Cats: treatment of biting lice infestations (*Felicola subrostratus*); Dogs: treatment of biting lice infestations (*Trichodectes canis*); Dogs: treatment of sarcoptic mange (caused by *Sarcoptes scabiei*); Dogs: treatment of adult intestinal roundworms (*Toxocara canis*).

## Additional benefits

The addition of new single-dose pipette sizes for larger cats and dogs simplifies selection of the correct dose for these animals.

## Risk assessment

Main potential risks:

*Quality:*

The formulation and manufacture of the new strengths are the same as for the authorised presentations of Stronghold which is well described and specifications set will ensure that product of consistent quality will be produced. The shelf life and storage precautions for the new strengths have been justified.

*For the target animal:*

The product formulation, indications and dosing regimen have not changed. Given that dosing of cats weighing over 7.5 kg and dogs over 40 kg is already permitted based on a minimum dose of 6 mg/kg, it is considered that the safety profile of the new presentations in the target animals is the same as for the authorised presentations.

*For the user:*

The new presentations do not pose an unacceptable risk to the user when used in accordance with the SPC.

*For the environment:*

The new presentations of Stronghold are not expected to pose a risk for the environment when used according to the SPC. The standard advice for the disposal of any unused product or waste material included in the product literature is also applicable.

*Resistance:*

Development of resistance is of concern in general. Reduction of the possibility of misuse or unnecessary use is the most important factor in diminishing selection pressure for resistance.

## *Risk management or mitigation measures*

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

## Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The formulation and manufacture of the new presentations, i.e. 360 mg strength for dogs in a 3 ml pipette, and 60 mg strength for cats in a 1 ml pipette, are the same as for the existing presentations of Stronghold which are well-described. Quality issues specific to the new presentations, such as stability of the new 3 ml pipette, have been satisfactorily addressed by the provision of adequate data and the specifications set will ensure that a product of consistent quality will be produced.

The target animal safety and efficacy of the strengths of 360 mg for dogs and 60 mg for cats is supported by safety and efficacy data previously assessed, and the benefit-risk balance for these aspects therefore remains favourable.

Stronghold is well tolerated by the target animals and presents a low risk for users and the environment.

## *Conclusion on benefit-risk balance*

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and other product information.

## *Conclusion*

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP concluded that the quality, safety and efficacy of Stronghold were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the grouped extension for Stronghold.