22 May 2019
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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use

# CVMP assessment report for EVICTO (EMEA/V/C/004973/0000)

Name of active substance: selamectin

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

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# Introduction

The applicant Virbac S.A. submitted on 19 July 2018 an application for a marketing authorisation to the European Medicines Agency (The Agency) for EVICTO through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed upon by the EMA/CVMP on 15 February 2018 as the product would constitute a generic of a product authorised through the centralised procedure (Stronghold).

The proposed indications are:

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 3 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 week 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 area to which the animal has access.
- Prevention of heartworm disease caused by *Dirofilaria immitis* with monthly administration. The product may be safely administered to animals infected with adult heartworms, however, it is recommended, in accordance with good veterinary practice, that all animals 6 months of age or more living in countries where a vector exists should be tested for existing adult heartworm infections before beginning medication with the product. 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 the product has been administered monthly. This product is not effective against adult *D. immitis.*
- Treatment of ear mites (*Otodectes cynotis*).

Cats:

- Treatment of biting lice infestations (*Felicola subrostratus*).
- Treatment of adult roundworms (*Toxocara cati*).
- Treatment of adult intestinal hookworms (*Ancylostoma tubaeforme*).

Dogs:

- Treatment of biting lice infestations (*Trichodectes canis*).
- Treatment of sarcoptic mange (caused by *Sarcoptes scabiei*).
- Treatment of adult intestinal roundworms (*Toxocara canis*).

The active substance of EVICTO is selamectin, a semi-synthetic compound of the avermectin class that paralyses and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death. The target species are cats and dogs.

EVICTO spot on is packed in single-dose pipettes containing 15 mg, 30 mg, 45 mg, 60 mg, 120 mg, 240 mg or 360 mg of selamectin and are presented in packs containing 1, 4 or 24 pipettes.

The rapporteur appointed is Jeremiah Gabriel Beechinor and the co-rapporteur is Hanne Bergendahl.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application.

On 22 May 2019, the CVMP adopted an opinion and CVMP assessment report.

On 19 July 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for EVICTO.

### *Scientific advice*

Not applicable.

### *MUMS/limited market status*

Not applicable.

## Part 1 - Administrative particulars

### *Detailed description of the pharmacovigilance system*

The applicant has provided a detailed description of the pharmacovigilance system (version 2.8; dated 05/12/2017) which fulfils the requirements of Directive 2001/82/EC. 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 Community or in a third country.

In order to facilitate adverse event surveillance it is recommended that the periodic safety update report (PSUR) submission cycle for this generic product be aligned with that of the reference product Stronghold to allow synchronisation of PSUR submissions in the future. In addition, surveillance of data in EudraVigilance Veterinary (EVVet) should also be synchronised for signal detection of the two products.

### *Manufacturing authorisations and inspection status*

Batch release takes place at Virbac S.A., Carros, France. The site has a manufacturing authorisation issued on 13$^{th}$ June 2018 by Agence Nationale du Médicaments Vétérinaire (Anses ANMV), France. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for batch release of such veterinary dosage forms, has been provided. The site is considered appropriately certified as complying with GMP requirements.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

### *Overall conclusions on administrative particulars*

The detailed description of the pharmacovigilance system was considered in line with legal

requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

# Part 2 - Quality

## *Composition*

The finished product is presented as spot-on solutions containing either 60 mg/ml or 120 mg/ml of selamectin as active substance.

Other ingredients are: butylhydroxytoluene, dipropylene glycol methyl ether and isopropyl alcohol.

The product is available in 1 ml or 3 ml polypropylene single-dose pipettes which contain 0.25 ml, 0.75 ml or 1.0 ml of the 60 mg/ml selamectin solution (equivalent to 15 mg, 45 mg or 60 mg of selamectin respectively) or 0.25 ml, 0.5 ml, 1.0 ml, 2.0 ml or 3.0 ml of the 120 mg/ml selamectin solution (equivalent to 30 mg, 60 mg, 120 mg, 240 mg or 360 mg of selamectin respectively).

## *Containers*

The primary packaging is 1 ml or 3 ml polypropylene single-dose pipettes. Secondary packaging consists of aluminium sachets consisting of polyethylene terephthalate / aluminium / polyethylene, which is placed in an outer carton. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements.

The outer cardboard cartons contain one, four or twenty-four pipettes.

## *Development pharmaceutics*

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

The proposed formulations of the generic product were developed to be pharmaceutically equivalent to those of the reference product, based on publicly available information and reverse engineering studies on the reference product. In line with the reference product, polypropylene pipettes were chosen, with the same proposed delivered volumes as those of the reference products. The results of studies to determine the residual volume of the products in each size of container after expression of the dose have been provided, in line with the requirements of the “Guideline on the Quality Aspects of Single-dose Veterinary Spot-on Products” EMEA/CVMP/QWP/544461/2007.

## *Method of manufacture*

The manufacturing process consists of the preparation of a simple solution, stirred and filtered through a clarifying filter. The filling machine is adjusted for the expected extractable mass and the pipettes are filled, sealed and packed into aluminium sachets. The calculations necessary to adjust the fill volumes are in line with the requirements of the “Guideline on the Quality Aspects of Single-dose Veterinary Spot-on Products” EMEA/CVMP/QWP/544461/2007, along with the calculations for targeted extractable mass. The process is considered to be a standard manufacturing process.

A process validation study has been provided for the manufacturing process. In general, it has been

demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and the pharmaceutical form.

## *Control of starting materials*

## *Active substance*

Selamectin is a semi-synthetic product derived from a fermentation product of the avermectin class.

The active substance is a hygroscopic powder that is practically insoluble in water but is freely soluble in isopropyl alcohol.

There is a monograph of selamectin in the Ph. Eur., and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for selamectin, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional VICH GL18 compliant specifications have been set for residual solvents, using the limits and test method as per the Ph. Eur. CEP. The active substance is in solution in the finished products, and so physico-chemical characteristics such as polymorphism and particle size are not relevant for this dosage form.

Batch analysis data from three batches of the active substance from the proposed supplier have been provided. The results are within the specifications.

Stability data on 3 batches of active substance from the proposed manufacturer, stored in the intended commercial package for 24 months under long term conditions at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines, were provided.

The following parameters were tested: appearance, water, related substances, and assay, identification, heavy metals, sulphated ash, residual solvents and microbial quality at the initial time-point, at the 6 month time-point at 40°C/75% RH, and up to the 24 month time-points at 25°C/60%RH. The analytical methods used were the same as for the active substance specification and were stability indicating, along with the necessary test methods and validation that were provided for the microbial quality testing.

All tested parameters were within the specification. Degradation products showed minor increasing trends under long-term and accelerated conditions but remained within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months, with no special storage precautions in the proposed container.

## *Excipients*

All excipients are well known pharmaceutical ingredients. The excipients butylhydroxytoluene and isopropyl alcohol are compliant with their Ph. Eur. monographs. The excipient dipropylene glycol methyl ether is not monographed in the Ph. Eur. and acceptable in-house specifications have been provided. The list of excipients is included in section 6.1 of the SPC.

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

None of the starting materials used for the active substance 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). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

## *Control tests during production*

Not applicable.

## *Control tests on the finished product*

The specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.

The analytical methods used have been provided and in general are adequately described. The methods are appropriately validated in accordance with the VICH guidelines. Appropriate information regarding the reference standards used for finished product testing has been provided.

Batch analysis results are provided for bulk batches of the 60 mg/ml (all three of which were filled into finished product sub-batches of 0.25 ml, 0.75 ml and 1.0 ml fill sizes) and of the 120 mg/ml products (all three of which were filled into finished product sub-batches of 0.25 ml, 0.5 ml, 1.0 ml, 2.0 ml and 3.0 ml fill sizes). All of the batches were greater than 10% of the maximum batch size. The data confirmed the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

## *Stability*

Finished product stability data on 9 batches of the 60 mg/ml product, and 15 batches of the 120 mg/ml product, stored under long term conditions for up to 12 months at 30ºC/65% RH and for 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guideline GL3 were provided. All of the batches were greater than 10% of the maximum batch size. Bracketing and matrixing are employed. The batches of product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, related substances, assay per dosage unit, and assay of the antioxidant using the test methods detailed in Part II.E. Additional testing was included for colouration, deliverable mass, assay and microbial quality. These changes are included in the finished product shelf life specification. The proposed limits at shelf-life have also been justified.

The analytical procedures used are stability indicating. Trending of results was observed. But all results were within the proposed specifications. However, in accordance with the “Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products” EMEA/CVMP/QWP/846/99-Rev. 1, as updated stability data has only been provided to 12 months, a maximum shelf-life of 2 years is currently approvable, with no special requirement regarding storage temperature.

In addition, 1 batch each of the 60 mg/ml and the 120 mg/ml product were exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal

products. It was demonstrated that the product in the immediate packaging is sensitive to photo-degradation, but the product is photo-stable when kept in the secondary packaging.

### *Overall conclusions on quality*

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner, and compliance with the requirements of the Guideline on the Quality Aspects of Single-dose Veterinary Spot-on Products (EMEA/CVMP/QWP/544461/2007) has been demonstrated.

The information on the active substance selamectin is provided according to a Certificate of Suitability of the European Pharmacopoeia (CEP) for selamectin. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph with additional specifications in accordance with the Ph. Eur. CEP. The stability data provided justifies the proposed retest period of 30 months, with no special storage precautions in the proposed container.

Data has been presented to give reassurance on TSE safety.

For the finished product, the specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.

With respect to the veterinary product as packaged for sale, with stability data only provided to 12 months, a maximum shelf-life of 2 years is currently approvable, with no special requirement regarding storage temperature.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Based on the review of the data on quality, the manufacture and control of the product are considered to be acceptable.

## Part 3 – Safety

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic veterinary medicinal product). The reference product, Stronghold spot-on solution, has been authorised in the European Community for greater than 10 years and can be accepted as a valid reference product (originally authorised on 25/11/1999). The applicant claims that the quantitative and qualitative composition of the candidate formulation is identical to the reference product Stronghold and both candidate and reference products have the same pharmaceutical form. The applicant has applied for a waiver from bioequivalence studies in accordance with section 7.1.d of the Guideline on the conduct of bioequivalence studies for VMPs (EMA/CVMP/016/00-Rev.2);

*"The formulations are identical (identical active substances and excipients as well as physicochemical properties [e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process]). "*

However, the CVMP considers that the waiver from bioequivalence should be based on 7.1.b of the above guideline which states;

*"for products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cased when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in*

*the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance."*

Based upon the data, regarding the formulation and excipients, provided in Part II of the dossier, the CVMP considers that the criteria detailed in section 7.1.b of the aforementioned guideline have been satisfied.

Accordingly, given that bioequivalence has been claimed and it is argued that the test product is a generic of the reference product, cross-reference to the safety and efficacy parts of the dossier of the reference product is considered appropriate.

## *Pharmacodynamics*

Reference is made to the pharmacodynamic properties as detailed in section 5.1 of the SPC of the reference product:

Selamectin is a semi-synthetic compound of the avermectin class. Selamectin paralyses and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death.

Selamectin has adulticidal, ovicidal and larvicidal activity against fleas. Therefore, it effectively breaks the flea life cycle by killing adults (on the animal), preventing the hatching of eggs (on the animal and in its environment) and by killing larvae (environment only). Debris from selamectin-treated pets kills flea eggs and larvae not previously exposed to selamectin and thus may aid in the control of existing environmental flea infestations in areas to which the animal has access.

Activity has also been demonstrated against heartworm larvae.

## *Pharmacokinetics*

Reference is made to the pharmacokinetic properties as detailed in section 5.2 of the SPC of the reference product.

## *Absorption*

Following spot on administration selamectin is absorbed from the skin reaching maximum plasma concentrations approximately 1 and 3 days after administration in cats and dogs respectively.

## *Distribution*

Following absorption from the skin selamectin distributes systemically.

## *Metabolism*

Selamectin does not undergo extensive metabolism.

## *Excretion*

Selamectin is slowly eliminated from plasma as manifested in detectable plasma concentrations in dogs and cats 30 days after administration of a single topical dose at 6 mg/kg. The prolonged

persistence and slow elimination of selamectin from plasma is reflected in the terminal elimination half-life values of 8 and 11 days in cats and dogs respectively. The systemic persistence of selamectin in plasma and the lack of extensive metabolism provide effective concentrations of selamectin for the duration of the inter-dosing interval (30 days).

## *Toxicological studies*

No data presented.

## *User safety*

The applicant has not provided a user risk assessment. The candidate formulation is claimed to be identical and is accepted as being sufficiently similar to be considered the same as the reference product. In addition, it is highlighted that the candidate and reference formulations have the same pharmaceutical form and the candidate product is intended for the same indications, at the same dose rate as approved for the reference product. As such, it can be assumed that the safety profile for the user of the product and those in contact with recently treated animals are the same as for the reference product.

The Safety Expert proposes that the same risk mitigation measures that have been approved for the reference product also be included in the SPC proposed for the candidate product;

- 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 treated 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 product with caution.

Based on the high content of isopropyl alcohol solvent, the warning ‘The product is a skin and eye irritant’ has been included and clarifies the reasons for the subsequent risk mitigation advice.

This is considered appropriate. Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with recommendations included in the SPC.

## *Environmental risk assessment*

A Phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines. The environmental assessment can conclude at Phase I, question 3, as the VMP will be used

only in non-food animals. The omission of a Phase II assessment can be accepted. The environmental precaution statements proposed by the applicant for inclusion in SPC sections 4.5 and section 6.6 are the same as those previously agreed by the CVMP for the reference products and can therefore be applied to the candidate products.

The CVMP concludes that the candidate formulation will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

## *Overall conclusions on the safety documentation*

An exemption from the requirement to demonstrate *in-vivo* bioequivalence has been granted in accordance with section 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

The qualitative details of the reference product formulations and the quantitative details of the active substance and antioxidant are publicly available from the published SPCs of the reference product. Results of 'reverse engineering' studies have been provided in order to determine the product compositions with respect to the remaining excipients, namely; isopropyl alcohol and dipropylene glycol methyl ether. This has resulted in a candidate formulation which is sufficiently similar to the reference formulation to be considered the same. Hence bioequivalence with the reference product can be accepted.

Pharmacology

No data in relation to the pharmacological aspects of the product have been provided. As bioequivalence with the reference product is accepted, the omission of pharmacological data can be accepted.

The applicants' proposal to include the same information as that approved for the reference product in sections 5.1 and 5.2 of the proposed SPC is considered acceptable.

User Safety

No user safety assessment was provided.

The candidate formulation is claimed to be identical to the reference product. In addition, it is highlighted that the candidate and reference formulations have the same pharmaceutical form and the candidate product is intended for the same indications, at the same dose rate as approved for the reference product. As such, it can be assumed that the safety profile for the user of the product and those in contact with recently treated animals will be the same as that for the reference product.

The applicant has proposed including the same user safety warnings as approved by the CVMP for the reference product and this is considered appropriate. In addition, clarification that the product is a skin and eye irritant has been introduced in order to justify the safety warnings.

It can be accepted that the candidate formulation will not present an unacceptable risk to the user when stored, handled administered and disposed of in accordance with the recommendations included in the proposed SPC.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

# Part 4 – Efficacy

## *Pharmacodynamics*

See Part 3.

## *Development of resistance*

Given the legal basis of this application (generic) and the fact that the candidate formulation is claimed to be bioequivalent to the reference product and is to be applied to the same target species for the same indications at the same posology using the same route of administration, the potential for resistance development is not expected to differ between candidate and reference formulations.

As no new information has been identified from the published literature review that would suggest any changes in current knowledge on resistance development from that available at the time of authorisation of the reference product, the CVMP is of the opinion that there is no need to include any specific information on resistance in the proposed SPC.

## *Pharmacokinetics*

See Part 3.

## *Dose justification/determination*

The product is a topical spot-on formulation containing selamectin as the active substance, to be administered to cats and dogs at a minimum dose rate of 6 mg/kg of selamectin, with a minimum treatment interval of 1 month. The posology is justified by reference to the authorised SPC of the reference product.

## *Target animal tolerance*

The candidate formulations are generic products of Stronghold spot-on solutions. Article 13 of Directive 2001/82/EC states: "…the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community."

However, according to Commission Directive 2009/9/EC, for generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies, is required. Based upon the data provided in Part 2 of the dossier, it can be accepted that both candidate and reference formulations are of the same qualitative and quantitative composition regarding the active ingredient (selamectin) and the antioxidant (butylhydroxytoluene), given that this information is publicly available from the SPC of the reference product.

Results of 'reverse engineering' studies have been provided in order to determine the product compositions with respect to the remaining excipients, namely isopropyl alcohol and dipropylene glycol methyl ether. Based upon the results of those studies, it can be accepted that the formulations of the candidate and reference products are sufficiently similar to be considered the same.

Further, it can be accepted that they have the same pharmaceutical form, i.e. spot-on solution for topical application, and are to be used in the same target species, for the same indications, at the same doses. In addition, the same pipette sizes are proposed for the candidate product as approved for the reference product.

Given the above, the CVMP concludes that no difference between candidate and reference formulations in respect of target animal tolerance at the administration site is to be expected and the omission of formulation-specific tolerance data can be accepted.

It may be concluded that the candidate formulation will not present an unacceptable risk for the animal when administered in accordance with the recommendations included in the proposed SPC.

## *Clinical studies*

No clinical study data has been provided.

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product).

The applicant has claimed a waiver from the requirement to conduct bioequivalence studies in accordance with section 7.1.d of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

However, the CVMP considers that the waiver from bioequivalence should be based on 7.1.b of the aforementioned guideline. Based upon the data provided in Part 2 of the dossier, the CVMP considers that the criteria detailed in section 7.1.b of the guideline have been satisfied.

Given that the formulations of the candidate and reference products are sufficiently similar to be considered the same, the candidate product is expected to be as efficacious as the reference product for the proposed indications when administered in accordance with the recommendations included in the proposed SPC. Consequently, the omission of clinical study data can be accepted.

## *Overall conclusion on efficacy*

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product).

The applicant has been granted a waiver from the requirement to conduct bioequivalence studies in accordance with section 7.1.b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

Based upon the data provided in Part 2 of the dossier, it is considered that the criteria detailed in section 7.1.b of the aforementioned guideline have been satisfied, that is the candidate and reference formulations are sufficiently similar to be considered the same.

Consequently, results of pre-clinical and clinical efficacy studies have not been provided.

Given the legal basis of this application and the fact that bioequivalence between candidate and reference formulations is accepted, the omission of efficacy studies is considered to be acceptable.

# Part 5 – Benefit-risk assessment

## *Introduction*

EVICTO spot-on solution contains selamectin, which is a well-known active substance.

Selamectin is a semi-synthetic compound of the avermectin class that paralyses and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death. The product is intended for use in cats and dogs for treatment and/or prevention of different species of fleas, worms, lice and mites.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (application for a generic medicinal product).

## *Benefit assessment*

### Direct therapeutic benefit

The evidence for the direct therapeutic benefit of EVICTO has been supported based on a claim of bioequivalence to the reference product. The product is beneficial in the treatment and prevention of flea infestations caused by *Ctenocephalides* spp. in dogs and cats, prevention of heartworm disease caused by *Dirofilaria immitis* in dogs and cats, treatment of ear mites (*Otodectes cynotis*) in dogs and cats, biting lice infestations caused by *Felicola subrostratus* in cats and *Trichodectes canis* in dogs, adult roundworms in cats (*Toxocara cati*) and dogs (*Toxocara canis*), adult intestinal hookworms in cats (*Ancylostoma tubaeforme*) and sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs.

### Additional benefits

No additional benefits for this generic veterinary medicinal product have been identified, other than the availability of an alternative product on the market place.

### Risk assessment

Given that bioequivalence with the reference product has been accepted, the risks associated with use of the product are expected to be the same as those of the reference product. Therefore, the product is not expected to present an unacceptable risk to the target animal, user or environment when used as recommended.

As possible risks to the user are identified in the SPC of the reference product and as selamectin is known to be toxic to aquatic life, suitable risk mitigation measures and advice have been included in the proposed SPC (in line with what has been approved for the reference product) and this is considered adequate to mitigate the potential risks.

As with all parasiticides, use of the product may select for resistance of the target parasites but there is little evidence that this is occurring within the EU for selamectin. As the product is only intended for administration to non-food producing species, there are no consumer safety issues.

## *Risk management or mitigation measures*

Since bioequivalence between candidate and reference formulations has been accepted, it is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the SPC reflect those approved for the reference product. It is accepted that, for the risks identified in the SPC approved for the reference product, the same appropriate risk mitigation measures have been proposed for this generic product.

## *Evaluation of the benefit-risk balance*

Since the benefit/risk balance of the reference product has previously been judged to be favourable, and bioequivalence between candidate and reference product is accepted, it is accepted that the benefit/risk balance for this product is also favourable. Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk to the user, target species or the environment when used in accordance with the approved SPC and it is expected to be as efficacious as the reference product. Appropriate precautionary measures have been included in the SPC and other product information.

## *Conclusion*

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for EVICTO is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.