Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Imidamox 40 mg/10 mg Spot-on Solution for Small Dogs
Imidamox 100 mg/25 mg Spot-on Solution for Medium Dogs
Imidamox 250 mg/62.5 mg Spot-on Solution for Large Dogs
Imidamox 400 mg/100 mg Spot-on Solution for Extra-Large Dogs

Date Created: January 2020

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Imidamox 40 mg/10 mg Spot-on Solution for Small Dogs Imidamox 100 mg/25 mg Spot-on Solution for Medium Dogs Imidamox 250 mg/62.5 mg Spot-on Solution for Large Dogs Imidamox 400 mg/100 mg Spot-on Solution for Extra-Large Dogs
Applicant	Billev Farmacija Vzhod d.o.o. Ulica Parmova 14 Ljubljana SI-1000 Slovenia
Active substance	Imidacloprid, moxidectin
ATC Vetcode	QP54AB52
Target species	Dogs
Indication for use	For dogs suffering from, or at risk from, mixed parasitic infections. The treatment and prevention of flea infestation (*Ctenocephalides felis*). The treatment of biting lice (*Trichodectes canis*). The treatment of ear mite infestation (*Otodectes cynotis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*). The prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*). Treatment of circulating microfilariae (*Dirofilaria immitis*). The treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*). The prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*). The reduction of circulating microfilariae (*Dirofilaria repens*). The prevention of angiostrongylosis (L4 larvae

	and immature adults of *Angiostrongylus vasorum*). The treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*. The prevention of spirocercosis (*Spirocerca lupi*). The treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults). The treatment of the eye worm *Thelazia callipaeda* (adults). Treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara canis, Ancylostoma caninum* and *Uncinaria stenocephala*, adults of *Toxascaris leonina* and *Trichuris vulpis*). The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC, as amended.
Date of conclusion of the procedure	14th January 2020

I. SCIENTIFIC OVERVIEW

These were determined as generic 'hybrid' applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended, because bioequivalence with a reference product could not be demonstrated or inferred through bioavailability studies from bioequivalence study requirements. The reference products are Advocate Spot-on Solutions for Extra Large/Large/Medium/Small Dogs, authorised in the UK (EU) since April 2003. A biowaiver was granted under section 7.1 of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2; April 2011) Chapter 7. Waivers from bioequivalence study requirements for immediate release formulations.

The products are indicated for use in dogs, for the treatment of mixed parasite infections, as described in the Summary of Product Characteristics (SPC). The recommended minimum doses are 10 mg/kg bodyweight imidacloprid and 2.5 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight. (One pipette per treatment).

The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation. See the SPC for detail on the use of the product for the treatment of various target parasites.

The products are produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the products can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [1] of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain imidacloprid and moxidectin in varying quantities, (depending on the size of the dog treated), and the excipients benzyl alcohol, propylene carbonate, butylhydroxytoluene and trolamine.

Small dogs: ≤ 4 kg
Medium dogs: >4-10 kg
Large dogs: >10-25 kg
Extra large dogs: >25-40 kg

The container/closure system consists of a polypropylene unit dose pipette with polyethylene or polyoxymethylene or polypropylene closure with spike, packed into a laminated triplex bag composed of polyester, aluminium and polyetylene. Cardboard boxes contain 1, 3, 4, 24 or 48 pipettes. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of antimicrobial preservative are justified.

The products are an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: mixing of the ingredients, filtration and packaging of the products

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are imidacloprid and moxidectin, established active substances described in the European Pharmacopoeia, (Ph. Eur) The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. Certificates of Suitability were provided.

Excipients are described in the Ph. Eur. Benzyl alcohol also complies to the tighter limit for impurity A.

Packaging is suitably manufactured.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance, when stored under the approved conditions. Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

- Store in the original package in order to protect from moisture and light. This veterinary medicinal product does not require any special temperature storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

No pharmacological or toxicological data were required to be submitted for assessment for this section.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:,

- In order to prevent children from getting access to pipettes, keep the pipette in the original packaging until ready for use and dispose of used pipettes immediately.
- Do not ingest. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- People with a known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
- In very rare cases the product may cause respiratory irritation in sensitive individuals.
- If the product accidentally gets into eyes, they should be thoroughly flushed with water.
- Avoid contact with skin, eyes or mouth.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- Wash hands thoroughly after use.
- If skin or eye symptoms persist, seek medical advice immediately and show the package leaflet or label to the physician.
- Do not eat, drink or smoke during application.
- Treated animals should not be handled, especially by children, until the application site is dry. Therefore, it is recommended to apply the product in the evening. Recently treated animals should not be allowed to sleep in the same bed as their owner, especially children.

Environmental Safety

A Phase I Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The SPC carries the following information:

Pharmacodynamics

Imidacloprid, 1-(6-Chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it is more accurately described as a chloronicotinyl nitroguanidine. Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product. Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptors and the postulated poor penetration through the blood-brain barrier in mammals, it has virtually no effect on the mammalian CNS. Imidacloprid has minimal pharmacological activity in mammals.

Moxidectin, 23-(O-methyloxime)-F28249 alpha is a second-generation macrocyclic lactone of the milbemycin family. It is a parasiticide which is active against many internal and external parasites. Moxidectin is active against larval stages of *Dirofilaria immitis* (L1, L3, L4) and *Dirofilaria repens* (L1, L3). It is also active against gastrointestinal nematodes. Moxidectin interacts with GABA and glutamate-gated chloride channels. This leads to opening of the chloride channels on the postsynaptic junction, the inflow of chloride ions and induction of an irreversible resting state. The result is flaccid paralysis of affected parasites, followed by their death and/or expulsion.

The drug has a persistent action and protects dogs for 4 weeks after a single application against re-infection with the following parasites: *Dirofilaria immitis, Dirofilaria repens, Angiostrongylus vasorum.*

Pharmacokinetics

After topical administration of the product, imidacloprid is rapidly distributed over the animal's skin within one day of application. It can be found on the body surface throughout the treatment interval. Moxidectin is absorbed through the skin, reaching maximum plasma concentrations approximately 4 to 9 days after treatment in dogs. Following absorption from the skin, moxidectin is distributed systemically throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month. The $T_{1/2}$ in dogs is about 28.4 days. Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in dogs.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application.

Resistance

The SPC carries suitable warnings with regard to resistance:

Brief contact of the animal with water on one or two occasions between monthly treatments is unlikely to significantly reduce the efficacy of the product. However, frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product. Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time. Efficacy against adult *Dirofilaria repens* has not been tested under field conditions.

IV.II. Clinical Documentation

Clinical studies were not required due to the nature of the application.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics the benefit/risk profile of the products is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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