Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Endectrid 40 mg + 10 mg Spot-On Solution for Small Dogs
Endectrid 100 mg + 25 mg Spot-On Solution for Medium Dogs
Endectrid 250 mg + 62.5 mg Spot-On Solution for Large Dogs
Endectrid 400 mg + 100 mg Spot-On Solution for Extra-Large Dogs

Date Created: February 2015

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Endectrid 40 mg + 10 mg Spot-On Solution for Small Dogs Endectrid 100 mg + 25 mg Spot-On Solution for Medium Dogs Endectrid 250 mg + 62.5 mg Spot-On Solution for Large Dogs Endectrid 400 mg + 100 mg Spot-On Solution for Extra-Large Dogs
Applicant	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury Berkshire RG14 1JA - UK
Active substance	Imidacloprid Moxidectin
ATC Vetcode	QP54AB52
Target species	Dogs
Indication for use	• For the treatment and prevention of flea infestation (*Ctenocephalides felis*), • the treatment of biting lice (*Trichodectes canis*), • the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*), • the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*), • the 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),** • the 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). *,** new indication added via variation procedure, July 2018. Suitable data provided.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

These were generic applications for multi-strength products, for which the reference products were the comparable products for Advocate Spot-on Solution for Dogs, available in the UK since April 2003. (The reference products are the proposed products under a different name). The product is indicated for dogs suffering from or at risk from mixed parasitic infections: flea infestation (*Ctencephalides felis*), biting lice (*Trichodectes canis*) ear mite infestation (*Otodectes cynotis*), sarcoptic mange (*Sarcoptes scabiei* var. *canis*), demidicosis (*Demodex canis*), and prevention of heartworm diease (L3 and L4 larvae of *Dirofilaria immitis*. In addition, treatment of circulating microfilariae (*Dirofilaria immitis*), the treatment of cutaneous dirofilariosis, (adult stages of *Dirofilaria repens*), prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*), reduction of circulating microfilariae (*Dirofilaria repens*), prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*). The product also treats *Angiostrongylus vasorum* and *Crenosoma vulpis* and prevents infection with *Spirocerca lupi* (spirocercosis). Treatment of infection with L4 larvae, immature adults and adults of *Toxocara canis*, A*ncylostoma caninum* and *Uncinaria stenocephala* is also an indication, as is treatment of adults of *Toxascaris leonina* and *Trichuris vulpis*. New indications were added in July 2018 for the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults), and eyeworm *Thelazia callipaeda* (adults). Suitable data were provided. The product may be used as part of a treatment strategy for flea allergy dermatitis.

The recommended doses are as follows:

40 mg + 10 mg spot-on solution for small dogs 0.4 ml pipette, imidacloprid 10 mg/kg bodyweight, moxidectin 2.5 mg/kg bw.

100 mg + 25 mg spot-on solution for medium dogs 1.0 ml pipette, imidacloprid 10-25 mg/kg bodyweight, moxidectin 2.5-6.5 mg/kg bw.

250 mg + 62.5 mg spot-on solution for large dogs 2.5 ml pipette, imidacloprid 10-25 mg/kg bodyweight, moxidectin 2.5-6.25 mg/kg bw.

400 mg + 100 mg spot-on solution for extra-large dogs 4 ml pipette, imidacloprid 10-16 mg/kg bodyweight, moxidectin 2.5-4 mg/kg bw.

(Imidacloprid is toxic for birds, especially canaries).

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.[1] The products are safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain imidacloprid and moxidectin at varying concentrations, and the excipients are butylhydroxytoluene E321, benzyl alcohol and propylene carbonate.

The container/closure system consists of white screw-cap polypropylene pipettes containing various quantities of product. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified. The product is 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 products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines. The manufacturing process is a sequential dissolution process. Benzyl alcohol is stirred and butylhydroxytoluene added. Propylene carbonate is added, followed by the active substances. The product is filtered and filled into the appropriate containers.

II.C. Control of Starting Materials

The active substances are imidacloprid and moxidectin, established active substances. Moxidectin is described in the European Pharmacopoeia (Ph. Eur), and is produced in accordance with a Certificate of Suitability. Imadacloprid is controlled by an in-house specification. The active substances are manufactured in accordance with the principles of good manufacturing practice. Each excipient

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

is monographed (benzyl alcohol and butylhydroxytoluene E 321: Ph. Eur.; propylene carbonate: United States Pharmacopeia).

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.

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

The tests performed during production are described and the results of 3 consecutive runs, (3 older batches, 3 new batches), conforming to the specifications, are provided. The intermediate product can be stored for up to 12 months, (with additional benzaldehyde testing during development).

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. Tests on the finished product include those for clarity, colour, identity, density, water content, purity, uniformity of content and microbiological quality.

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.

Active Substances

For moxidectin, stability data were provided for 3 batches of product stored in commercial packaging under suitably controlled conditions. The product was stored in refrigerated conditions for 24 months (2-8^{o}C), and for 24 months at 25^{o}C/60% RH. Data supported a retest at the refrigerated temperature for 2 years. For imidacloprid, 3 commercial batches were stored at 25^{o}C/60% RH and 40^{o}C/75% RH for 24 months and 12 months respectively. The active substance was very stable with no special storage conditions required. The proposed retest period of 2 years was satisfactory.

Finished products

Batches were stored at 25°C/60% RH, 30°C/50% RH, 30°C/80% RH and 40°C/75% RH. All data were considered acceptable.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13 (1), and bioequivalence with a reference product has been established, results of safety and residues tests were not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Documentation

User Safety

A User Risk Assessment was not submitted with these applications. Because the products are identical to the reference product, this was acceptable. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Safety

Phase I:

An extended Phase I risk assessment was provided. 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 products are intended only for non-food producing species. As dogs may enter water courses, the following warnings are included in the SPC:

- Any unused product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

- The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Dogs should not be allowed to swim in surface waters for 4 days after treatment.

IV CLINICAL DOCUMENTATION

As these were generic applications according to Article 13 (1), and bioequivalence with a reference product has been established, efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

No data were submitted, however, relevant data reflects that of the reference product, and this is acceptable.

Imadacloprid is an ectoparasiticide which belongs to the chloronicotinyl group of compounds, effective against a variety of parasites. Inhibition of cholinergic transmission results in paralysis and death of the parasite. There is virtually no effect on mammalian cholinergic transmission due to the weak interaction of the active substance with mammalian nicotinergic receptors and probable poor penetration of the blood-brain barrier.

Moxidectin is a second generation macrocyclic lactone belonging to the milbemycin family, and is a parasiticide interacting with GABA[3] and glutamate-gated chloride channels. This ultimately causes flaccid paralysis of parasites, followed by death or expulsion.

Pharmacokinetics

No data were submitted, however, relevant data reflects that of the reference product, and this is acceptable.

Imidacloprid is rapidly absorbed via the skin and can be located on the body surface during the treatment interval. Moxidectin is also absorbed through the skin, attaining maximum plasma concentrations approximately 4-9 days after treatment. Systemic distribution follows, followed by slow elimination. Refer to section 5.2 of the SPC for further information.

[3] GABA – gamma-amino butyric acid.

Tolerance in the Target Species

No data were submitted. Warnings in the SPC reflect those of the reference products.

Resistance

The applicant provided an update on the resistance in the target parasites. The SPC carries suitable warnings, which define the possibility of resistance developing to the products. It is advised that local epidemiological information be taken into account when the products are prescribed.

IV.II. Clinical Documentation

As the products were established as being bioequivalent to the reference products, no further data were required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) 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.

(www.gov.uk/check-animal-medicine-licensed)

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.

(www.gov.uk/check-animal-medicine-licensed)