Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

Date: 22 November 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0196/003/MR DE/V/0196/004/MR DE/V/0196/005/MR DE/V/0196/006/MR
Name, strength and pharmaceutical form	Prinovox 40 mg + 10 mg Spot-On Solution for Small Dogs Prinovox 100 mg + 25 mg Spot-On Solution for Medium Dogs Prinovox 250 mg + 62.5 mg Spot-On Solution for Large Dogs Prinovox 400 mg +100 mg Spot-On Solution for Extra-Large Dogs
Applicant	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany
Active substance(s)	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).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	22nd February 2017
Date product first authorised in the Reference Member State (MRP only)	17th December 2014 in UK
Concerned Member States for original procedure	France, Ireland, Italy, Portugal, Spain, United Kingdom (former RMS)

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. Bioequivalence is accepted in accordance with section 7.1(d) of the current 'guideline for the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.2) because the applicant is the MAH of the reference product and the formulations are identical.

The products are indicated for dogs suffering from or at risk from mixed parasitic infections: flea infestation (*Ctenocephalides felis*), biting lice (*Trichodectes canis*) ear mite infestation (*Otodectes cynotis*), sarcoptic mange (*Sarcoptes scabiei* var. *canis*), demodicosis (*Demodex canis*), and prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*. In addition, treatment of circulating microfilariae (*Dirofilaria immitis*), 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*, prevents infection with *Spirocerca lupi* (spirocercosis) and treats the lungworm *Eucoleus* (syn. *Capillaria*) *boehmi* (adults) and the eye worm *Thelazia callipaeda (adults)*. 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*. 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.

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

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

guidelines. The manufacturing process is sequential dissolution followed by filtration and filling.

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 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.

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 (2-8ºC), and for 24 months at

25ºC/60% RH. Data supported a retest at the refrigerated temperature for 2 years.

For imidacloprid, 3 commercial batches were stored at 25ºC/60% RH and 40ºC/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 25ºC/60% RH, 30ºC/50% RH, 30ºC/80% RH and 40ºC/75% RH. All data were considered acceptable.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Do not store above 25ºC.

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. The warnings and precautions as listed on the product literature are identical to the reference product:

- Avoid contact with skin, eyes or mouth.
- Do not eat, drink or smoke during application.
- Wash hands thoroughly after use.
- After application do not stroke or groom animals until the application site is dry.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- 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.
- If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or label to the physician.

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.
- Moxidectin fulfils the criteria for a persistent, bioaccumulative and toxic substance; therefore, exposure of the environment to moxidectin should be minimised as much as possible. The product should not enter water courses as it has harmful effects on aquatic organisms. Moxidectin is highly toxic to 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.

Imidacloprid 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.

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.

[3] GABA – gamma-amino butyric acid.

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section 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.

•	Approved 22 November 2021	Changes to the product literature (Summary of Product Characteristics (SPC) section 4.6 and Package Leaflet (PL) section 6 of a generic medicinal product following assessment of the same change for the reference product DE/V/0196/003-006/IB/004
•	26 April 2021	Addition of new therapeutic indications in cats for the prevention of lungworm disease (L3/L4 larvae of Aelurostrongylus abstrusus), the treatment of the lungworm Aelurostrongylus abstrusus (adults) and the treatment of the eye worm Thelazia callipaeda (adults)DE/V/0196/001-002/IB/003
•	08 June 2020	MA transfer in DE (Bayer Vital GmbH to Elanco GmbH)
•	17 December 2019	Renewal of the Marketing authorisation DE/V/0196/001-006/R/001
•	23 April 2018	Change in RMS from UK to DE.
•	Approved 11 April 2018	Addition of new therapeutic indication for the treatment of . the lungworm Eucoleus (syn. Capillaria) boehmi and the eye worm Thelazia callipaeda in dogs UK/V/0619/003-006/IB/004
•	Approved 08 December 2017	Change in the address of the marketing authorisation holder from Bayer plc, Animal Health Division, Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA to Bayer plc, 400 South Oak Way, Green Park, Reading, Berkshire, RG2 6AD. UK/V/xxxx/IA/0144/G
•	Approved 03 August 2017	Change in the name of a manufacturer used in the manufacture of the active substance. UK/V/0619/003-006/IA/002
•	Approved 12 May 2017	Change in the number of units (e.g. tablets*, ampoules*, etc.) in a pack outside the range of the currently approved pack sizes of the finished product.

		UK/V/0619/003-006/IB/001
•	22 February 2017	MRP (UK as RMS)
•	24 May 2016	Changes to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH
•	18 May 2016	Change in the SPC, labelling or package leaflet following assessment of the same change for the reference product.
•	25 August 2015	Change in test procedure for the finished product.
•	30 July 2015	Addition of a manufacturing site for secondary packaging.
•	30 June 2015	Submission of an updated certificate of suitability.