Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Imidaflea 40 mg Spot-on Solution for Small Cats, Small Pet Rabbits & Small Dogs
Imidaflea 80 mg Spot-on Solution for Large Cats and Large Pet Rabbits
Imidaflea 100 mg Spot-on Solution for Medium Dogs
Imidaflea 250 mg Spot-on Solution for Large Dogs
Imidaflea 400 mg Spot-on Solution for Extra Large Dogs

Date Created: July 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Imidaflea 40 mg Spot-on Solution for Small Cats, Small Pet Rabbits & Small Dogs Imidaflea 80 mg Spot-on Solution for Large Cats and Large Pet Rabbits Imidaflea 100 mg Spot-on Solution for Medium Dogs Imidaflea 250 mg Spot-on Solution for Large Dogs Imidaflea 400 mg Spot-on Solution for Extra Large Dogs
Applicant	EU Pharmaceuticals Ltd 37 Geraldine Road London SW18 2NR United Kingdom
Active substance	Imidacloprid
ATC Vetcode	QP53AX17
Target species	Dogs, Cats and Pet Rabbits
Indication for use	Cats & Pet Rabbits: Prevention and treatment of flea (*Ctenocephalides felis*) infestations. Dogs: For the prevention and treatment of flea infestations and for the treatment of biting lice (*Trichodectes canis*).

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	Generic-Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	2nd July 2019

I. SCIENTIFIC OVERVIEW

These were generic 'hybrid' applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended. The reference products are:

- Advantage 40 mg Spot-on Solution for Small Cats, Small Dogs and Pet Rabbits
- Advantage 80 mg Spot-on Solution for Large Cats and Pet Rabbits
- Advantage 100 mg Spot-on Solution for Dogs
- Advantage 250 mg Spot-on Solution for Dogs
- Advantage 400 mg Spot-on Solution for Dogs

The reference products have been authorised in the UK since 1999.

These were determined generic 'hybrid' applications because bioequivalence with the reference products could not be demonstrated for these topically applied products. The principles of the biowaivers stated in the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) were applied. The applicant claimed exemption from *in vivo* studies in accordance with Section 7.1.d) of this guideline. The proposed products are quantitatively and qualitatively identical to the reference product in terms of active substances. In terms of excipients, the proposed and reference products are qualitatively identical, but not quantitatively identical. Differences in the quantitative composition of excipients are not expected to influence the absorption and distribution of active substances in the proposed products, compared to that of the reference products. Therefore, the products can be used interchangeably, and target animal safety and efficacy for the proposed products were inferred from that of the reference products.

These products are spot-on solutions and contain either 40 mg, 80 mg, 100 mg, 250 mg or 400 mg of the active substance imidacloprid to treat cats, rabbits and dogs of various sizes. The proposed indications are for the prevention and treatment of flea *(Ctenocephalides felis)* infestations in cats, the treatment of flea

infestations in rabbits and for the prevention and treatment of flea infestations and for the treatment of biting lice *(Trichodectes canis)* on dogs. The proposed dosage is one pipette per animal of the specified weight or two pipettes of the largest size for dogs weighing ≥ 40 kg as a single treatment. This gives a minimum dose of 10 mg imidacloprid per kg bodyweight.

The products are administered topically as a spot-on, dosed according to body weight.

The product is 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 product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] of the product 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 are unit-dose pipettes containing different volumes of solution comprising imidacloprid as the active substance with benzyl alcohol and propylene carbonate as co-solvents. Butylhydroxytoluene is incorporated as an antioxidant, with the solution being manufactured and filled under a Nitrogen atmosphere.

The container/closure system consists of single use pipettes comprising a plastic (300 µm) laminate material consisting of three layers: polypropylene / cyclic olefin copolymer / polypropylene together with a copolymer (70 µm) of polyethylene /ethylene vinyl alcohol / polyethylene. Polyethylene is in direct contact with the finished product.
Pipettes are provided in individual sachets comprising either:
Sachet A - 12 µm polyethylene / 12 µm low density polyethylene / 7 µm aluminium foil / 18 µm low density polyethylene / 40 µm linear low-density polyethylene, or Sachet B - 12 µm polyethylene terephthalate / 9 µm aluminium / 15 µm oriented polyamide / 100 µm white linear low-density polyethylene.
Cartons containing 1, 2, 3, 4 or 6 pipettes.

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

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 product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of three stages synthesis of N-(imidazolidin-2-ylidene)nitramide, synthesis of imidacloprid, and purification of imidacloprid.

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

II.C. Control of Starting Materials

The active substance is imidacloprid a long-established active substance, but it does not appear in a pharmacopoeial monograph, it is controlled by in-house specification. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification based on that found in the active substance master file (ASMF) is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. Certificates of analysis were also provided.

Imidacloprid is packaged in a low-density polyethylene plastic bag, which is placed inside a fibre drum. It is packaged in pack sizes of 1, 5, 10 and 25kg.

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. Control tests on the finished product are those for appearance, identification, assay, uniformity of dosage form, seal integrity test, microbial purity, total aerobic microbial count (TAMC) and total yeast / mould count (TYMC).

II.F. Stability

Stability data on the active substance 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

The veterinary medicinal products do not require any special storage conditions.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological and Toxicological Studies

The applications have been made in accordance with Article 13(3) as bioequivalence cannot be demonstrated. However, the applicant claims the products are quantitively and qualitatively identical to the reference products; therefore, no pharmacological or toxicological data were submitted. Any differences in excipients between the products and the reference products are unlikely to impact on user safety, the products are intended to be used in the

same species, at the same dose and administered the same way as the reference products.

User Safety

The applicant states that the products have been formulated with qualitatively and quantitatively identical active substance and excipients to the reference product. The pharmaceutical form, target species and dose rate are also considered identical. Therefore, no qualitative or quantitative risk assessment has been provided.

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:

- This product can cause mucous membrane, skin and eye irritation, therefore, contact of the product with mouth, skin and eyes should be avoided.
- This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions in rare cases (for example, irritation, tingling).
- People with a known hypersensitivity (allergy) to insecticides or alcohol should avoid contact with the product.
- Do not smoke, drink or eat during application.
- If contact with the skin occurs, wash hands with soap and water.
- If the product gets into eyes, the eyes should be thoroughly rinsed with clean water. If skin or eye irritation persists, or the product is accidentally swallowed, seek medical advice.
- Do not stroke, groom or play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals are not allowed to sleep with owners, especially children.
- Dispose of used pipettes immediately.
- Wash hands after use.

Environmental Safety

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

Phase I:
A Phase I environmental risk assessment was submitted, the applicant has correctly shown that the assessment concludes at question 3 of the decision

tree. 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.

IV. CLINICAL DOCUMENTATION

Pharmacology

The applications were submitted under Article 13(3); this is appropriate because the products are topically applied for local action and so bioequivalence cannot be demonstrated or inferred.
However, the proposed products contain the same active substance as the reference products, and so the pharmacodynamic and pharmacokinetic properties of imidacloprid are established. Section 5.1 of the proposed SPCs contains the same information as that of the reference products.

Tolerance in the Target Species

Both the proposed and reference products are: for use in the same target species; presented in single-use pipettes for topical administration; administered in the same manner; quantitatively the same in terms of active substance per dose; qualitatively the same in terms of excipients. Based on this, and that any small quantitative differences in terms of excipients would be unlikely to impact on the rate or extent of bioavailability or local tolerance of the active substance, it was accepted that no tolerance data have been provided.

Resistance

The applications were submitted in accordance with Article 13(3) of Council Directive 2001/82/EC, as amended by 2004/28/EC, therefore no data were presented. There is no known resistance to imidacloprid in Europe.

IV.II. Clinical Documentation

The applications have been submitted under Article 13(3); this is appropriate because the product is topically applied for local action and so bioequivalence cannot be demonstrated or inferred. According to this article, the results of appropriate pre-clinical tests or clinical trials should be provided in this case. However, the guideline on the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/EWP/005/2000 Rev.3) provides the following option with the aim of reducing the number of clinical trials and to avoid

unnecessary use of animals in experiments for generic antiparasitic products with local activity:
'*Efficacy or tolerance studies are not considered necessary in the case that the composition (i.e. quality and quantity of the active substance(s) and excipient(s)) and the physico-chemical properties of the generic product and the reference product are identical, and the generic is to be administered at the same dose and route of administration as the reference product. If there is a difference in the qualitative or quantitative composition of the excipients which may affect absorption, the rate and extent of distribution and persistence of the active substance, further studies, e.g. dose confirmation and/or field studies, may be necessary.'*
Both the proposed and reference products are: for use in the same target species; presented in single-use pipettes for topical administration; administered in the same manner; quantitatively the same in terms of active substance per dose; qualitatively the same in terms of excipients. Based on this and that any small quantitative differences in terms of excipients would be unlikely to impact on the rate or extent of bioavailability of the active substance, it was accepted that that no clinical data were necessary.

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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