ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Advantage 40 mg Feline and Bunny Spot-On Solution [UK]
Advantage 40 mg Spot-On Solution for Small Cats and Small Pet Rabbits
[AT, DE, FR, IE, IT]

Advantage 80 mg Feline and Bunny Spot-On Solution [UK]
Advantage 80 mg Spot-On Solution for Large Cats and Large Pet Rabbits
[AT, DE, FR, IE, IT]

PuAR correct as of 21/08/2018 when RMS was transferred to AT.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0389/001/DC UK/V/0389/002/DC
Name, strength and pharmaceutical form	Advantage 40 mg Feline and Bunny Spot-On Solution Advantage 80 mg Feline and Bunny Spot-On Solution
Applicant	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury Berkshire RG14 1JA
Active substance(s)	Imidacloprid
ATC Vetcode	QP53AX17
Target species	Cats and pet rabbits
Indication for use	<u>Advantage 40 mg Feline and Bunny Spot-On Solution</u> For cats of less than 4 kg: Prevention and treatment of flea infestations For pet rabbits of less than 4 kg: Treatment of flea infestations. <u>Advantage 80 mg Feline and Bunny Spot-On Solution</u> For cats of 4 kg and greater: Prevention and treatment of flea infestations. . For pet rabbits of 4 kg and greater: Treatment of flea infestations. Fleas are killed within one day following treatment. One treatment prevents further flea infestation for three to four weeks on cats and up to one week on pet rabbits. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in cats, where this has been previously diagnosed by a veterinary surgeon.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Applications in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	26 October 2011
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Austria France Germany Ireland Italy

I. SCIENTIFIC OVERVIEW

These applications for generic products were submitted in accordance with Article 13 (1) of Directive 2001/82/EC. The reference products are Advantage 40 mg spot-on solution for small cats, small dogs and pet rabbits and Advantage 80 mg spot-on solution for large cats and pet rabbits, authorised in the UK since August 2001 and July 2003 respectively. The applicant also referred to Advantage 40 for cats and Advantage 80 for cats, authorised in the UK since March 1997.

Advantage 40 mg feline and bunny spot-on solution and Advantage 80 mg feline and bunny spot-on solution are indicated for use in cats and pet rabbits. Advantage 40 mg feline and bunny spot-on solution is indicated for the prevention and treatment of flea infestations in cats of less than 4 kg bodyweight and treatment of flea infestations in pet rabbits of less than 4 kg bodyweight. Advantage 80 mg feline and bunny spot-on solution is indicated for the prevention and treatment of flea infestations in cats of more than 4 kg bodyweight and treatment of flea infestations in pet rabbits of more than 4 kg bodyweight. A 1 x 0.4 ml pipette of Advantage 40 mg feline and bunny spot-on solution is used for animals below 4 kg in bodyweight. A 1 x 0.8 ml pipette of Advantage 80 mg feline and bunny spot-on solution is used for animals equivalent to, or over 4 kg in bodyweight. Fleas are killed within one day following treatment. One treatment prevents further flea infestation for three to four weeks on cats and up to one week on pet rabbits. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in cats, where this has been previously diagnosed by a veterinary surgeon.

The products are produced and controlled using validated methods and tests, which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species; the slight 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 of each product was demonstrated according to the claims made in the SPC.

II. QUALITY ASPECTS

A. Composition

Advantage 40 mg Feline and Bunny Spot-On Solution

Each 0.4 ml pipette contains 40 mg imidacloprid as an active substance and butylhydroxytoluene E321, benzyl alcohol E1519 and propylene carbonate as excipients. The container/closure system consists of white polypropylene pipettes each containing 0.4 ml solution. The pipettes are contained in blister packs holding 2, 3, 4 or 6 unit dose pipettes.

[1] SPC - Summary of Product Characteristics

Advantage 80 mg Feline and Bunny Spot-On Solution
Each 0.8 ml pipette contains 80 mg imidacloprid as an active substance and butylhydroxytoluene E321, benzyl alcohol and propylene carbonate as excipients. The container/closure system consists of white polypropylene pipettes each containing 0.8 ml solution. The pipettes are contained in blister packs holding 2, 3, 4 or 6 unit dose pipettes.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation is justified.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance, imidacloprid, has no monograph in the European Pharmacopoeia. The manufacturer provided details of a testing monograph, and this was considered acceptable. The active substance is manufactured in accordance with the principles of good manufacturing practice.

There are three excipients used in the formulation. Butylhydroxytoluene E321 and benzyl alcohol have monographs in the European Pharmacopoeia and each complies with the requirements of the current edition of the Ph. Eur. Propylene carbonate does not have a Ph. Eur. monograph. However, it is tested against the USPNF[2] specification, and additional tests for appearance, content of propylene oxide, propylene glycol and water. This is considered acceptable.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

The tests performed during production are described and the results conforming to the specifications are provided.

[2] United States Pharmacopeia and The National Formulary

F. 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.

G. Stability

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. The shelf-life of the veterinary medicinal product as packaged for sale is 5 years.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life

- Shelf life of the veterinary medicinal product as packaged for sale: 5 years

Special precautions for storage

- This veterinary medicinal product does not require any special storage conditions.
- Keep the blister in the outer carton

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

These applications for generic products were submitted in accordance with Article 13 (1) of Directive 2001/82/EC. The applicant cross-referred to Advantage 40 mg spot-on solution for small cats and pet rabbits and Advantage 80 mg spot-on solution for large cats and rabbits, authorised in the UK since August 2001 and 2003 respectively. The applicant also referred to Advantage 40 for cats and Advantage 80 for cats, which were authorised in the UK in March 1997. The formulations for these products are identical to reference products and therefore bioequivalence studies were not required.

User Safety

A user risk assessment was provided. The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Do not massage the application site.
- This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions in rare cases (for example, irritation, tingling).
- Avoid contact between the product and skin, eyes or mouth.
- Do not eat, drink or smoke during application.
- Wash off any skin contamination with soap and water.
- If the product gets into eyes accidentally, the eyes should be thoroughly flushed with water.
- If skin or eye irritation persists, obtain medical attention.
- If the product is accidentally swallowed, obtain medical attention immediately.
- Wash hands thoroughly after use.
- After application, do not stroke or groom animals until application site is dry.
- People with known hypersensitivity to imidacloprid should avoid contact with the veterinary medicinal product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that no extensive exposure of the environment would occur due to use of the products, and this was acceptable

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Not applicable as the products are intended for administration to non-food species only.

IV CLINICAL ASSESSMENT (EFFICACY)

These applications for generic products were submitted in accordance with Article 13 (1) of Directive 2001/82/EC. The applicant cross-referred to Advantage 40 mg spot-on solution for small cats and pet rabbits and Advantage 80 mg spot-on solution for large cats and rabbits, authorised in the UK since August 2001 and 2003 respectively. The applicant also referred to Advantage 40 for cats and Advantage 80 for cats, which were authorised in the UK in March 1997. The formulations for these products are identical to reference products. Therefore these products were assumed bioequivalent to reference products and no further data was submitted. This is considered acceptable.

IV.A Pre-Clinical Studies

Resistance

The applicant was unable to locate any references in the literature relating to resistance against this active substance despite more than 10 years of use. This is considered acceptable and no further data was required.

IV.B Clinical Studies

These applications for generic products were submitted in accordance with Article 13 (1) of Directive 2001/82/EC. The applicant cross-referred to Advantage 40 mg spot-on solution for small cats and pet rabbits and Advantage 80 mg spot-on solution for large cats and rabbits, authorised in the UK since August 2001 and 2003 respectively. The applicant also referred to Advantage 40 for cats and Advantage 80 for cats, which were authorised in the UK in March 1997. The formulations for these products are identical to reference products. Therefore these products were assumed bioequivalent to reference products and no further data was submitted. This is considered acceptable.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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)