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

Johnson's 4fleas 40 mg Spot-on Solution for Dogs up to 4 kg
Johnson's 4fleas 100 mg Spot-on Solution for Dogs of 4 kg up to 10 kg
Johnson's 4fleas 250 mg Spot-on Solution for Dogs of 10 kg up to 25 kg
Johnson's 4fleas 400 mg Spot-on Solution for Dogs over 25 kg
(United Kingdom)

Advantage Flea Control 40 mg Spot-on Solution for Small Dogs
Advantage Flea Control 100 mg Spot-on Solution for Medium Dogs
Advantage Flea Control 250 mg Spot-on Solution for Large Dogs
Advantage Flea Control 400 mg Spot-on Solution for Extra-Large Dogs
(Ireland)

Updated: February 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0507/003/DC UK/V/0507/004/DC UK/V/0507/005/DC UK/V/0507/006/DC
Name, strength and pharmaceutical form	Johnson's 4fleas 40 mg Spot-on Solution for Dogs up to 4 kg Johnson's 4fleas 100 mg Spot-on Solution for Dogs of 4 kg up to 10 kg Johnson's 4fleas 250 mg Spot-on Solution for Dogs of 10 kg up to 25 kg Johnson's 4fleas 400 mg Spot-on Solution for Dogs over 25 kg
Applicant	Bayer plc 400 South Oak Way Green Park Reading Berkshire RG2 6AD
Active substance(s)	Imidacloprid
ATC Vetcode	QP53AX17
Target species	Dogs
Indication for use	For the prevention and treatment of flea infestations and for the treatment of biting lice (*Trichodectes canis*) on dogs. Fleas are killed within one day following treatment. One treatment prevents further flea infestation for four weeks.

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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23rd April 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Ireland

I. SCIENTIFIC OVERVIEW

Johnson's 4fleas 40 mg, 100 mg, 250 mg and 400 mg Spot-on Solutions for use in dogs have been developed as generics of Advantage 40, 100, 250 and 400 Spot-on Solutions. The reference products have been authorised in the UK since March 1997. Bioequivalence with the reference product is claimed on the basis that the products are identical in composition and posology.

The products have been developed as spot-on solutions indicated for the prevention and treatment of flea and biting lice infestations in dogs weighing below 4 kg (40 mg), dogs weighing 4kg up to 10 kg (100 mg), large dogs weighing 10 kg up to 25 kg (250 mg) and very large dogs weighing 25 kg or more (400 mg). The products are contraindicated in unweaned puppies of less than 8 weeks of age and in animals with known hypersensitivity to the active substance or any excipient.

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; the slight 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 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.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains the active substance imidacloprid and the excipients butylhydroxytoluene E321, benzyl alcohol E1519 and propylene carbonate.

The container/closure system consists of a white polypropylene pipette closed with a cap. The 40 mg and 100 mg solution are in 1 ml pipettes, the 250 mg in a 2.5 ml pipette and the 400 mg in a 4 ml pipette. The pipettes are packaged in blisters containing 1, 2, 3, 4 or 6 pipettes and supplied in a carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the excipients before adding imidacloprid and stirring until fully dissolved. The solution is then filtered and filled into large containers before transfer into the single-dose pipettes which are then heat sealed. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is imidacloprid, an established active substance not described in the European Pharmacopoeia. An in-house specification has been provided for the active substance manufacturer. 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.

The excipients butylhydroxytoluene and benzyl alcohol comply with their respective Ph. Eur. monographs. Propylene carbonate is not described in a pharmacopeia and the specification has been submitted. Certificates of analysis have been provided for all excipients.

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 of 3 consecutive runs, conforming to the specifications, are provided.

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. The tests include those for identification and assay of the active substance and excipients, clarity, colour, density, refractive index, extractable volume and content uniformity.

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.

G. 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. The stability studies show imidacloprid is very stable and a retest period of 2 years has been established.

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. Data have been provided for the product stored at 25°C/60%RH, 30°C/50%RH and 30°C/80%RH for 60 months as well as batches stored at 40°C for up to 12 months and 4°C for 12 months. A shelf life of 5 years is supported.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 5 years.
- This veterinary medicinal product does not require any special temperature storage conditions.
- Keep the blister in the outer carton.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product, the results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product, the results of toxicological studies are not required.

User Safety

The applicant has not provided a user safety assessment in compliance with the relevant guideline as the application has been submitted as a generic according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product. The user risks are the same as those identified for the reference product and therefore the same warnings and precautions are listed on the product literature and are adequate to ensure safety to users of the product.

- Wash hands thoroughly after use.
- Wash off any skin contamination with soap and water.
- People with known skin sensitivity may be particularly sensitive to this product.
- Avoid contact of the product with the eyes or mouth.
- After application, do not stroke or groom pets until application site is dry.
- If the product gets into eyes accidentally, the eyes should be thoroughly flushed with water. If skin or eye irritation persists, or the product is accidentally swallowed, obtain medical attention.
- Do not eat, drink or smoke during application.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that as the product is for use in non-food animals only it will pose minimal risk to the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product, the results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product, the results of tolerance studies are not required.

Resistance

The information provided suggests that there is no indication of a recent change to the susceptibility patterns of fleas or biting lice to the active substance. As such the same warnings and precautions as cited on the reference product appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed due to the nature of the product, the results of laboratory trials are not 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 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)