MEB agency / Veterinary Medicinal Products Unit
The Netherlands

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Combotec 50 mg/60 mg Spot-on Solution for Cats and Ferrets
Combotec 67 mg/60.3 mg Spot-on Solution for Small Dogs
Combotec 134 mg/120.6 mg Spot-on Solution for Medium Dogs
Combotec 268 mg/241.2 mg Spot-on Solution for Large Dogs
Combotec 402 mg/361.8 mg Spot-on Solution for Extra Large Dogs

Created: 22Jan2024

PRODUCT SUMMARY

EU procedure number	NL/V/0251/001-005/DC
Name, strength and pharmaceutical form	Combotec 50 mg/60 mg Spot-on Solution for Cats and ferrets Combotec 67 mg/60.3 mg Spot-on Solution for Small Dogs Combotec 134 mg/120.6 mg Spot-on Solution for Medium Dogs Combotec 268 mg/241.2 mg Spot-on Solution for Large Dogs Combotec 402 mg/361.8 mg Spot-on Solution for Extra Large Dogs
Applicant	Beaphar B.V. Drostenkamp 3 8101 BX, Raalte The Netherlands
Active substance(s)	fipronil, (S)-methoprene
ATC vet code	QP53AX65
Target species	Cats, ferrets, dogs
Indication for use	Combotec 50 mg/60 mg Spot-on Solution for Cats and ferrets In cats: • To be used against infestations with fleas, alone or in association with ticks and/or biting lice. • Elimination of fleas (Ctenocephalides spp.). Insecticidal efficacy against new infestations with adult fleas persists for 4 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity), larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for six weeks after application. • Elimination of ticks (Ixodes ricinus, Dermacentor variabilis, Rhipicephalus sanguineus). The product has a persistent acaricidal efficacy for up to 2 weeks against ticks (based on experimental data). • Elimination of biting lice (Felicola subrostratus). The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). In ferrets: • To be used against infestations with fleas, alone or in association with ticks.

	• Elimination of fleas (Ctenocephalides spp.). Insecticidal efficacy against new infestations with adult fleas persists for 4 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity), larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas. • Elimination of ticks (Ixodes ricinus). The product has a persistent acaricidal efficacy for 4 weeks against ticks (based on experimental data). Combotec 67 mg/60.3 mg Spot-on Solution for Small Dogs Combotec 134 mg/120.6 mg Spot-on Solution for Medium Dogs Combotec 268 mg/241.2 mg Spot-on Solution for Large Dogs Combotec 402 mg/361.8 mg Spot-on Solution for Extra Large Dogs **In dogs:** - To be used against infestations with fleas, alone or in association with ticks and/or biting lice. - Treatment of flea infestations (Ctenocephalides spp.). Insecticidal efficacy against new infestations with adult fleas persist for 8 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for eight weeks after application. - Treatment of tick infestations (Ixodes ricinus, Dermacentor variabilis, Dermacentor reticulatus, Rhipicephalus sanguineus) The product has a persistent acaricidal efficacy for up to 4 weeks against ticks. - Treatment of infestations with biting lice (Trichodectes canis). The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for these veterinary medicinal products (VMP) are available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Reference products (RP)	Frontline Combo Spot-on Hond S Frontline Combo Spot-on Hond M Frontline Combo Spot-on Hond L Frontline Combo Spot-on Hond XL Frontline Combo Spot-on Kat
RP Marketing authorisation holder	Boehringer Ingelheim B.V.
RP EU procedure number	FR/V/0139/001-005
RP date of authorisation	27 January 2004
Date of completion of the original decentralised procedure	20 November 2019
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	CZ, IT, HU, MT (and FR)
Withdrawn CMS during original decentralised procedure	FR: The company decided to withdraw the application. At the time of withdrawal, the MS considered that the data provided did not allow to conclude on a positive benefit-risk balance as potential serious risk to public health was raised, which was not supported by the RMS and other CMSs.

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be used safely in the target species; the reactions observed are indicated in the SPC.

The VMP 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 VMP has been demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis has been considered positive for granting marketing authorisations.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The spot-on solution for dogs contains 100.0 mg/ml fipronil and 90.0 mg/ml (S)-methoprene and is available in pipettes of 0.67 ml, 1.34 ml, 2.68 ml and 4.02 ml. The spot-on solution for cats and ferrets contains 100.0 mg/ml fipronil and 120.0 mg/ml (S)-methoprene and is available in pipettes of 0.5 ml. The container of all VMPs consists of blue pipette composed of a heat-formed shell (polypropylene-cyclic olefin copolymer-ethylene-vinyl alcohol copolymer/polypropylene) and a film (polyethylene terephthalate/aluminium/polypropylene). The blue pipette is enclosed in an aluminium blister (polyethylene / polyamide / aluminium / polyamide / polyethylene and polyamide / aluminium / polyethylene).

The choice of the formulations are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

C. Production and control of starting materials

The active substances are fipronil and (S)-methoprene, both established active substances. Fipronil is described in the European Pharmacopoeia. The active substances are 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.

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

D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

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 VMP.

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.

F. Stability tests

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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

The safety aspects of this product are identical to the reference product.

A. Safety tests

Pharmacological studies

The applicant made reference to the data that support the marketing authorisation of the reference product, Frontline Combo Spot-on (Boehringer Ingelheim Animal Health Netherlands B.V.). As this concerned a hybrid application in accordance with Article 13(3) of Directive 2001/82/EC, no pharmacological studies were required.

Toxicological studies

The applicant made reference to the data that support the marketing authorisation of the reference product, Frontline Combo Spot-on (Boehringer Ingelheim Animal Health Netherlands B.V.). As this concerned a hybrid application in accordance with Article 13(3) of Directive 2001/82/EC, no toxicological studies were required. However, bibliographic studies were provided, from which it could be concluded that: fipronil is acute toxic, it may cause severe acute effects after dermal absorption and it may cause neurotoxicity. (S)-methoprene is less toxic than fipronil. Some of the excipients may cause mild irritation or hypersensitivity reactions.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the VMP can cause mucous membrane, skin and eye irritation and allergic reactions upon contact, and the VMP can cause neurotoxicity and be harmful if swallowed.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the VMP will only be used in non-food animals.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, efficacy studies are not required.

The efficacy claims for this VMP are equivalent to those of the reference VMP.

As Combotec is a topically applied VMP which is not systemically acting, bio-equivalence has been positively assessed in accordance with the *Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats.* Eligibility for this bioequivalence exemption is supported by a comparative study of physic-chemicals analysis to establish similarity. The quality and quantity of the active substances and physico-chemical properties of the VMP are identical to those of the reference product. Potential differences regarding excipients do not affect the absorption, the rate and extent of distribution and persistence of the active substance.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated post-authorisation to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

Sequence of significant variations

None.