Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

VETERINARY MEDICINAL PRODUCT

WormScreen Tablets for Dogs

Date Created: July 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	WormScreen 50/144/150 mg Tablets for Dogs
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Praziquantel 50 mg Pyrantel Embonate 144 mg Febantel 150 mg
ATC Vetcode	QP52AC55
Target species	Dogs
Indication for use	For the treatment of mixed infestations with the following roundworms and tapeworms in adult dogs and puppies: Nematodes Ascarids: *Toxocara canis*, *Toxascaris leonina* (late immature forms and mature forms) Hookworms: *Uncinaria stenocephala*, *Ancylostoma caninum* (adults) Cestodes Tapeworms: *Taenia* spp., *Dipylidium caninum*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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 conclusion of the procedure	23rd July 2019

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Wormscreen Tablets for Dogs, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.

The product is indicated for the treatment of mixed infestations with the following roundworms and tapeworms in adult dogs and puppies:
Nematodes
Ascarids: *Toxocara canis*, *Toxascaris leonina* (late immature forms and mature forms)
Hookworms: *Uncinaria stenocephala*, *Ancylostoma caninum* (adults)
Cestodes
Tapeworms: *Taenia* spp., *Dipylidium caninum.*

The recommended dose rates are: 15 mg/kg bodyweight febantel, 14.4 mg/kg pyrantel and 5 mg/kg praziquantel. This is equivalent to 1 tablet per 10 kg bodyweight. Tablets may be halved/quartered to allow accuracy of dosing.

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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains pyrantel embonate (144 mg/tablet), praziquantel (50 mg/tablet), and febantel 150 mg /tablet), and the excipients lactose monohydrate, maize starch, povidone K-30, sodium lauryl sulfate, microcrystalline cellulose, colloidal Anhydrous Silica, magnesium stearate and meat flavour.

The container/closure system consists of an OPA/Al/PVC-Al blister in a cardboard box, containing 2 or 4 tablets. 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 is as follows: The active substances are mixed whilst a granulation liquid is prepared. Once the granulate has formed, it is dried and mixed with appropriate excipients and compressed before being suitably packaged for sale.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substances are established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance have been provided. Acceptable Certificates of Suitability were received.

All excipients except the meat flavouring are listed in the Ph. Eur. All packaging conforms to appropriate specifications and guidelines.

II.C.4. Substances of Biological Origin

Satisfactory documentation was received. With regard to lactose monohydrate, compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, uniformity of dosage units, water content, uniformity of mass, hardness, identification of active substances and related substances, content and dissolution of active substances and microbiological quality.

II.F. Stability

Stability data on the active substances has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

This medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended results of pharmacological or toxicological tests are not required. The product is of the same pharmaceutical form as the reference product and is used in the same species, for the same indications and at the same dose. Therefore, no pharmacological or toxicological data were required. A user risk assessment (URA) and environmental risk assessment were provided.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The following applicant's user recommendations are appropriate:

- In the interests of good hygiene, persons administering the tablet directly to a dog or by adding it to the dog's food, should wash their hands afterwards.
- In case of accidental ingestion, seek medical advice and show the package leaflet to the physician.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines. A Phase I ERA correctly concluded that the product, which is only to be used in individual dogs, is not expected to pose a risk to the environment when used as recommended.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

No pharmacological data were submitted. Pharmacodynamic and pharmacokinetic data were accepted as being the same as those of the reference product.

Pharmacodynamics

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended results of pharmacodynamic tests are not required. The product contains anthelmintics active against roundworms and tapeworms. The product contains three active substances: febantel, pyrantel embonate (pamoate) and praziquantel, a partially hydrogenated pyrazino-isoquinoline derivative used widely as an anthelmintic for both human and veterinary use. Pyrantel acts as a cholinergic agonist. Its mode of action is to stimulate nicotinic cholinergic receptors of the parasite, induce spastic paralysis and thereby allow removal from the gastro-intestinal (GI) system by peristalsis.

With the mammalian system febantel undergoes ring closure forming fenbendazole and oxfendazole. It is these chemical entities which exert the anthelmintic effect by inhibition of tubulin polymerization. Formation of microtubules is thereby prevented, resulting in disruption to structures vital to the normal functioning of the helminth. Glucose uptake, in particular, is affected,

leading to depletion in cell ATP. The parasite dies upon exhaustion of its energy reserves, which occurs 2 – 3 days later.

Praziquantel is very rapidly absorbed and distributed throughout the parasite. Both *in vitro* and *in vivo* studies have shown that praziquantel causes severe damage to the parasite integument, resulting in contraction and paralysis. There is an almost instantaneous tetanic contraction of the parasite musculature and a rapid vacuolisation of the syncytial tegument. This rapid contraction has been explained by changes in divalent cation fluxes, especially calcium.

In this fixed combination product pyrantel and febantel act synergistically against nematodes (ascarids and hookworms) in dogs. In particular, the activity spectrum covers *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala* and *Ancylostoma caninum*. The spectrum of activity of praziquntel covers also cestode species in dogs, in particular all *Taenia* spp. and *Dipylidium caninum*. Praziquantel acts against adult and immature forms of these parasites.

Pharmacokinetics

Praziquantel is absorbed almost completely from the intestinal tract when given orally. After absorption, the drug is distributed to all organs. Praziquantel is metabolized into inactive forms in the liver and secreted in bile. It is excreted within 24 hours to more than 95% of the administered dosage.

The pamoate salt of pyrantel has low aqueous solubility, an attribute that reduces absorption from the gut and allows the drug to reach and be effective against parasites in the large intestine. Because of the low systemic absorption of pyrantel pamoate, there is very little danger of adverse reactions/toxicity in the host. Following absorption, pyrantel pamoate is quickly and almost completely metabolized into inactive metabolites that are excreted rapidly in the urine.

Febantel is absorbed relatively rapidly and metabolized to a number of metabolites including fenbendazole and oxfendazole, which have anthelmintic activity.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application. The SPC and product literature carry suitable warnings with regard to transient digestive tract and neurological disorders

Resistance

Adequate warnings and precautions appear on the product literature:

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.

IV.II. Clinical Documentation

The applicant conducted four dose confirmation studies and supporting bibliographical data.

Dose confirmation studies:

Study title (1)	Evaluation of the efficacy of WormScreen Plus Flavour Tablets against *Dipylidium Caninum* in Naturally Infected Dogs - GCP[3] Study
Objectives	To evaluate the efficacy of WormScreen Tablets against *D. caninum* in line with the valid guidelines.
Test site(s)	Single-centre - third country.
Test Product	Investigational veterinary medicinal product (IVP) – WormScreen Tablets for Dogs
Control product/placebo	Negative control – no treatment.
Animals	24 crossbreed dogs, 6 or more months old. Dogs were naturally infected with *D caninum* and not treated with any anthelmintic within 10 days of acclimatisation start.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the IVP. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised according to bodyweight and gender.
Blinding	All investigational staff were blinded until study completion.
Method	On Day -7, all animals were treated for flea infestations which could allow reinfection with *D. caninum.* During a 7-day acclimatisation period, infection with *D. caninum* was confirmed. On Day 0, animals in treatment group were treated with WormScreen, at the recommended dose. Negative control group dogs were not treated. Following treatment, animals were observed hourly for 4 hours to check for signs of intolerance. On Day 10, all worms and scoleces were retrieved from the animals and preserved in formalin for later identification.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from the treatment group compared to the negative control group. A p value of <0.05 was used to determine statistical significance. Calculated efficacy of WormScreen Plus Flavour Tablets at least 90%.
RESULTS	No signs of intolerance were observed in either group. The IVP-treated group was found to be significantly

[3] GCP – Good Clinical Practice.

	different from the negative control group.
DISCUSSION	The applicant concluded that WormScreen Tablets is 100% effective in treating *D. caninum* infections and is well tolerated by dogs.

Study title (2)	Evaluation of the efficacy of WormScreen Plus Flavour Tablets against *Taenia Hydatigena* in Naturally Infected Dogs - GCP Study
Objectives	To evaluate the efficacy of WormScreen Tablets against *Taenia h.* in line with the valid guidelines.
Test site(s)	Single-centre - third country.
Test Product	Investigational veterinary medicinal product (IVP) – WormScreen Tablets for Dogs
Control product/placebo	Negative control – no treatment.
Animals	24 crossbreed dogs, . Dogs were naturally infected with *T. hydatigena* and not treated with any anthelmintic within 10 days of acclimatisation start.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the IVP. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised according to bodyweight and gender.
Blinding	All investigational staff were blinded until study completion
Method	On Day -7, all animals were treated for flea and tick infestations. During the 7-day acclimatisation period, infection with *T. hydatigena* was confirmed. On Day 0, animals in treatment groups were treated with WormScreen or comparator product, at the recommended dose. Negative control group dogs were not treated. Following treatment, animals were observed hourly for 4 hours to check for signs of intolerance. On Day 10, all worms and scoleces were retrieved from the animals and preserved in formalin for later identification.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from the treatment group compared to the negative control group. A p value of <0.05 was used to determine statistical significance. Calculated efficacy of WormScreen Plus Flavour Tablets at least 90%
RESULTS	Due to the method of administration being whole or half tablets, animals received doses of praziquantel varying from 5.10 to 7.20 mg/kg (mean 6.35 mg/kg) – IVP. No signs of intolerance were observed.

DISCUSSION	The applicant concluded that WormScreen Tablets is 100% effective in treating *T. hydatigena* infections and are is well tolerated by dogs.

Study Title (3)	Evaluation of the efficacy of WormsScreen Tablets against *Trichuris Vulpis* and Hookworms in naturally infected dogs – GCP study
Objectives	To evaluate the efficacy of WormScreen Tablets against *Trichuris vulpis* and hookworms in line with the valid guidelines.
Test site(s)	Single-centre - third country.
Test Product	Investigational veterinary medicinal product (IVP) – WormScreen Tablets for Dogs
Control product/placebo	Negative control – no treatment.
Animals	24 crossbreed dogs.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the IVP. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised according to bodyweight and gender.
Blinding	All investigational staff were blinded until study completion.
Method	During the 7-day acclimatisation period, infection with *T. vulpis* and *A. caninum* was confirmed. If present, *U. stenocephala* eggs were also counted and from these data, pre-treatment mean epg values were calculated for each worm species in each animal. On Day 0, animals in the treatment group were treated with WormScreen, at the recommended dose. Negative control group dogs were not treated. Following treatment, animals were observed hourly for 4 hours to check for signs of intolerance. On Day 7, faecal samples were collected from all animals for egg flotation counts again, all worms were retrieved from the animals and preserved in formalin for later identification.
Statistical method	Primary Parameter: Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from treatment groups compared to the negative control group. Secondary Parameter: Egg Reduction: the treatment group was compared to negative control for percentage egg reduction on Day 7. Percentage egg reduction on Day 7 was also calculated for treatment groups comparing with the pre-treatment mean. Significance was set at 5% ($p<0.05$). To be judged

	effective, the following conditions needed to be satisfied: • At least 6 animals in untreated group adequately infected with *T. vulpis, A. caninum* and, if applicable, *U. stenocephala*. • Statistically significant difference in parasite counts between treatment groups and untreated control group • Calculated efficacy of IVP at least 90%.
RESULTS	Due to the method of administration being whole or half tablets, animals received varying doses of pyrantel (for hookworms). The dose received of febantel (for *T. vulpis*) varied as well. For both *A. caninum* and *U. stenocephala* the treatment group was found to be significantly different from negative control. For *T. vulpis*, however, there was no significant difference between the treatment group and the untreated control group. Any adverse events were noted.
DISCUSSION	The applicant concluded that WormScreen Tablets is effective in treating *A. caninum*, *U. stenocephala* and *T. vulpis* infections and is well tolerated by dogs.

Study title (4)	Evaluation of the Efficacy of WormScreen Tablets against *Toxocara Canis* in naturally infected dogs - GCP study
Objectives	Assessment of efficacy.
Test site(s)	Single-centre - third country.
Test Product	Investigational veterinary medicinal product (IVP) – WormScreen Tablets for Dogs
Control product/placebo	Negative control – no treatment.
Animals	36 crossbreed dogs, younger than 6 months (mostly under 12 weeks) old
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the IVP. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised according to pre-treatment egg counts and gender.
Blinding	All investigational staff were blinded until study completion.
Method	During the 7 day acclimatisation period, infection with *T. canis* was confirmed and pre-treatment mean epg values were calculated for each animal. On Day 0, animals in treatment groups were treated with WormScreen, at the recommended dose. Negative

	control group dogs were not treated. Quartered tablets were given to dogs weighing less than 2kg. Following treatment, animals were observed hourly for 4 hours to check for signs of intolerance. From Day 0 to Day 7 total faeces were collected twice daily and examined macroscopically for parasites or segments of parasites and preserved in formalin for identification. On Day 7, faecal samples were collected from all animals for egg flotation counts again and all worms and scoleces were retrieved from the animals. They were preserved in formalin for later identification.
Statistical method	Primary Parameter: Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from the treatment group compared to the negative control group. Secondary Parameter: Egg Reduction: the treatment group was compared to negative control for percentage egg reduction on Day 7. Percentage epg reduction on Day 7 was also calculated for the treatment group comparing with the pre-treatment mean. Significance was set at 5% ($p<0.05$). To be judged effective, the following conditions needed to be satisfied: • At least 6 animals in untreated group adequately infected with *T. canis*. • Statistically significant difference in parasite counts between treatment groups and untreated control group • Calculated efficacy of IVP at least 90%.
RESULTS	Due to the method of administration being whole, half or quarter tablets, animals received variable doses of pyrantel. Any adverse events were noted. Regarding the controlled test, the treatment group was found to be significantly different from untreated control group ($p<0.0001$). Other species of worms found at necropsy were recorded but have not been subjected to statistical analysis.
DISCUSSION	The applicant concluded that WormScreen Tablets is effective in treating *T. canis* infections and that it is well tolerated by dogs.

Based on sufficient justification, the authorisation also includes an indication for *Toxocara leonina*.

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 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.

(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)