Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

WormScreen 230 mg/20 mg Film-coated Tablets for Cats

Date Created: April 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	WormScreen 230 mg/ 20 mg Film-coated Tablets for Cats
Applicant	Billev Farmacija Vzhod d.o.o. Parmova Ulica 14 1000 Ljubljana Osrednjeslovenska Slovenia
Active substance	Praziqiantel Pyrantel embonate
ATC Vetcode	QP52AA51
Target species	Cats
Indication for use	For the treatment of mixed infestations with roundworms, hookworms and tapeworms in cats, caused by: - adult stages of ascarids: *Toxocara cati (syn. mystax)* - adult stages of hookworms: *Ancylostoma tubaeforme, Ancylostoma braziliense* - tapeworms*: Echinococcus multilocularis, Dipylidium caninum, Hydatigera (Taenia) taeniaeformis, Mesocestoides spp., Joyeuxiella pasqualei.*

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	27th March 2019

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The product is indicated for use in cats, for the treatment of mixed infestations with roundworms, hookworms and tapeworms in cats, caused by: adult stages of ascarids: *Toxocara cati (syn. mystax),* adult stages of hookworms: *Ancylostoma tubaeforme, Ancylostoma braziliense,* and tapeworms*: Echinococcus multilocularis, Dipylidium caninum, Hydatigera (Taenia) taeniaeformis, Mesocestoides spp., Joyeuxiella pasqualei.*

The dose is 5 mg praziquantel and 20 mg pyrantel base (57.5 mg pyrantel embonate) per kg of body weight. This corresponds to 1 tablet per 4 kg of body weight. Kittens weighing less than 1 kg should not be treated with the product, because correct dosing of such cats may not be feasible.

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 CONSTIUENTS

II.A. Composition

The product contains 230 mg pyrantel embonate per tablet, (equivalent to 80 mg pyrantel) and 20 mg praziquantel. The excipients are maize starch, povidone K25, cellulose, microcrystalline (E460), silica (colloidal anhydrous), magnesium stearate (E572), hypromellose, macrogol 4000 and titanium dioxide (E171).

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

The container/closure system consists of Blister packs consisting of cold formed OPA/Aluminium/PVC foil and aluminium foil in a box. The box contains a blister with two 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 consists of a granulation, drying and sieving process, followed by mixing and compression and film-coating of the tablets.

Process validation data on the product have been presented in accordance with the relevant European guidelines. The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substances are pyrantel embonate and praziquantel, established active substance described in the European Pharmacopoeia (Ph. Eur). 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 and acceptable Certificates of Suitability have been provided.

All excipients are monographed within the Ph. Eur, and packaging meets the requirements of the Ph. Eur or relevant specifications.

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

The tests performed during production are suitably described.

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: appearance, uniformity of dosage units, identification, content and active substance related substances, dissolution of the active substances and microbiological quality.

II.F. Stability

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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life of halved tablets after first opening the immediate packaging: 1 month.
Store unused parts of the halved tablets below 25°C.
Each time an unused part-tablet is stored until next use, it should be returned to the open blister pocket and kept in a safe place out of the sight and reach of children.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application, no toxicological or pharmacological data were submitted. A user risk assessment (URA) and environmental risk assessment (ERA) were provided.

User Safety

A URA 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. Therefore the following applicant's user recommendations are appropriate:

- In case of accidental ingestion, seek medical advice and show the package leaflet to the physician.
- In the interest of good hygiene, persons administering the tablets directly to the cat or by adding them to the cat's food should wash their hands afterwards.
- Other precautions
- Echinococcosis represents a hazard for humans. As Echinococcosis is a notifiable disease to the World Organisation for Animal Health (OIE), specific guidelines on the treatment and follow-up, and on the safeguard of persons, need to be obtained from the relevant competent authority.

Environmental Safety

The ERA was carried out in accordance with VICH and CVMP guidelines.

Phase I:

A Phase I ERA was conducted. The 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

Dissolution studies performed comparing the proposed and reference product were acceptable, and sufficient data were provided in a bioequivalence study.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Pyrantel has a good activity against nematodes occurring in cats. The active substance acts as a cholinergic agonist similarly to nicotine, and causes spastic paralysis of the nematodes by a depolarising neuromuscular blockade.

Praziquantel is absorbed rapidly through the parasite's surface and is distributed evenly inside the parasite. Both *in vitro* and *in vivo* severe damage to the parasite integument sets in very quickly, resulting in contraction and paralysis of the parasites. The basis for the rapid onset of action is above all the praziquantel-induced change in the permeability of the parasite membrane to Ca^{++}, which leads to a dysregulation of the parasite metabolism.

Pharmacokinetics

Praziquantel is rapidly absorbed following oral administration. Maximum serum levels are achieved within 2 hours. Praziquantel is widely distributed and is rapidly metabolised in the liver. In addition to other metabolites, the main metabolite occurring in each case is the 4-hydroxycyclohexyl derivative of praziquantel. Praziquantel is completely eliminated within 48 hours in the form of its metabolites - between 40 and 71 % in the urine and, in bile, between 13 and 30 % in the faeces. The embonate salt of pyrantel is poorly absorbed from the gastrointestinal tract.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application.

Resistance

Suitable references were provided.
Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted a dose confirmation study.

Dose confirmation study:

Study title	A dose confirmation study of a single administration of an oral pyrantel and praziquantel formulation against adult *Echinococcus multilocularis* in experimentally infected cats
Objectives	Determination the efficacy of a single dose of an orally administered formulation, containing pyrantel/praziquantel combination, against *Echinococcus multilocularis* in experimentally infected cats.
Test site(s)	Third country test site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	Pyrantel/Praziquantel 230 mg/20 mg film-coated tablets for cats. Administered once daily on Day 0 to infected cats at a dose rate of 5 mg praziquantel and 57.5 mg pyrantel embonate per kg bodyweight, equivalent to 1 kg to 2 kg cats receiving half a tablet, and 2.1 to 4.0 kg cats receiving 1 tablet.
Control product/placebo	Negative control.
Animals	20 young animals, 10 in an untreated control group and 10 administered the proposed product. 5 males and 5 females in each group.
Outcomes/endpoints	% Reduction in target parasite.
Randomisation	Randomised.
Blinding	Parallel group designed blinded.
Method	Day -18. The cats were infected with approximately 20 000 *E. multilocularis* protoscoleces, from an isolate that was less than 10 years old. At Day 0, one tablet a day was provided to cats for 5 days.
Statistical method	SAS version 9.3 TS level 1M2 was used for all the statistical analyses. The level of significance for the formal test was set at 5%, all tests were two-sided. The differences in worm counts between treatment and control group were analysed by means of an ANOVA with a treatment

	effect after a logarithmic transformation of the worm (count +1) of the data. In addition, the groups were compared using an ANOVA with treatment effect on untransformed worm count data.
RESULTS	
Outcomes for endpoints	100 % of parasites were terminated in the group of animals given the proposed products. No adverse events were noted and the formulation was well-tolerated.
DISCUSSION	In light of the reference product demonstrating efficacy against all target parasite species, no further dose confirmation studies were 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 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.

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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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