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Publicly Available Assessment Report for a Veterinary Medicinal Product

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Pigfen 200 mg/ml suspension for use in drinking water for pigs

PRODUCT SUMMARY

EU Procedure number	IE/V/0577/001 (formerly UK/V/0643/001)
Name, strength and pharmaceutical form	Pigfen 200 mg/ml suspension for use in drinking water for pigs
Active substances(s)	Fenbendazole
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of Authorisation	31 January 2018 (UK) 29 March 2018 (IE)
Target species	Pigs
Indication for use	Treatment of pigs infected with *Ascaris suum* (adult, intestinal and migrating larval stages)
ATCvet code	QP52AC13
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Slovakia, Spain. UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was an application for a generic 'hybrid' product, submitted under Article 13 (3) of Directive 2001/82/EC, as amended. This was determined a generic 'hybrid' application because bioequivalence could not be demonstrated or inferred through bioavailability studies/waivers from bioequivalence study requirements. Suitable safety and residues tests, in addition to appropriate studies to demonstrate the efficacy of the product in pigs were accepted.
The reference products are Panacur Premix for Medicated Feeding Stuff, marketed in the UK since 1993, and, as part of the global MA, Panacur Aqua Sol 200 mg/ml Oral Suspension for Use in Drinking Water for Pigs and Chickens, marketed in the UK since 2011 is also cited.
The product is indicated for the treatment of pigs infected with *Ascaris suum* (adult, intestinal and migrating larval stages).
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. The product is safe for the user, the consumer of foodstuffs from treated animals 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.

II. QUALITY ASPECTS

II.A. Composition

The product contains fenbendazole, and the excipients sodium benzoate (E211), docusate sodium, povidone, hydrochloric acid (concentrated, for pH adjustment), and water for injections.
The container/closure system consists of a white cylindrical high-density polyethylene (HDPE) bottle, with a white polypropylene (PP) screw tamper-evident closure of 125 ml and 1 litre. A white rectangular HDPE bottle of 1 litre with vertically see-through bar with an LDPE insert, closed with a white PP tamper-evident screw cap with a LDPE sealing disk. Or, white HDPE canisters with a white HDPE ribbed tamper-evident screw cap of 2.5 litres and 5 litres.
The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence 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 the creation of a nanosuspension by the following method: Dissolution of the excipients, wetting and milling of fenbendazole concentrate, preparation of 200 mg/ml fenbendazole suspension and filling and labelling of bottles

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

II.C. Control of Starting Materials

The active substance is fenbendazole, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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.

All excipients are monographed within the Ph. Eur.

Supporting certificates of analysis/suitability were provided for all components of the product, including the packaging.

II.C.4. Substances of Biological Origin

All suppliers of tallow for the packaging confirmed that this item complied with the EDQM Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

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 site have been provided demonstrating compliance with the specification. Control tests on the finished

product include those for: appearance, identity and content of the active substance, related substances, particle size, fill volume and microbial contamination.

II.F. 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 retest period is five years.

Stability data on the finished product were received, but suitable warnings are included on the SPC and product literature with regard to storage and use.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 30 months
Shelf life after first opening the immediate packaging: 3 months.
Shelf life of the medicated drinking water: 24 hours.

Product as packed for sales and after first opening: Do not freeze. Protect from frost.
Medicated water: Do not freeze.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bioequivalence could not be demonstrated by equivalence studies, therefore, the application was accepted a generic 'hybrid' product. No pharmacological or toxicological data were required, due to the nature of the application.

Pharmacodynamics

Fenbendazole belongs to the benzimidazoles class of anthelmintic compounds. This class of pharmaceutical binds selectively to the β-tubulin causing the depolymerisation of microtubules and disruption of such related tubules in helminths. The active substance is commonly used for the treatment of gastrointestinal infections in many species and has broad-spectrum activity against all stages of gastrointestinal nematodes.

Pharmacokinetics

Summary reports from the relevant CVMP[1] maximum residue limit document and World Health organisation dossier were provided. Fenbendazole has low oral bioavailability. Regardless of the route of administration, the metabolic pathway for fenbendazole is similar in all mammalian species. It is metabolised to oxfendazole and then to oxfendazole sulfone. Elimination is primarily via the faecal route.

Toxocological Studies

Published data were provided on a single dose, and repeated dose of the active substance in a variety of laboratory species. Studies on reproductive toxicity, mutagenicity, carcinogenicity were also presented. The SPC reflects the requisite dose, and the active substance was assessed as not being mutagenic or carcinogenic. The SPC and product literature carry suitable warnings with regard to use of the product during pregnancy and lactation:

- Administration of fenbendazole (500 mg/kg) to sows between days 8 and 33 of pregnancy produced no foetal effects. The safety of the product has not been established during lactation. Use according to the benefit/risk assessment by the responsible veterinarian.

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

- Embryotoxic effects cannot be excluded. Pregnant women must take extra precautions when handling this veterinary medicinal product.
- This veterinary medicinal product may be toxic to humans after ingestion.
- This product may cause eye irritation.
- Contact with the skin and the eyes or accidental ingestion of the product should be avoided.
- Do not smoke, eat or drink when handling the veterinary medicinal product.
- Wear goggles and impervious gloves to avoid direct skin and eye contact with the product when handling or preparing medicated drinking water.
- In the event of accidental ingestion, rinse mouth with plenty of clean water and seek medical advice. In the event of accidental contact with the skin or eyes, rinse with plenty of clean water and seek medical advice
- Wash hands after use.

Environmental Safety

An Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The applicant has submitted a Phase I environmental risk assessment conducted in accordance with current VICH and CVMP guidance. The VICH decision tree has been followed through to Question 17 and the PEC_{soil} values for a range of usage scenarios in pigs were calculated and shown to be below the trigger threshold of 100 µg/kg.

Therefore, a Phase II assessment was not required. Suitable warnings appear on the SPC and product literature.

III.B.2 Residues documentation

Residue Studies

The applicant conducted appropriate residue depletion studies. A GLP-compliant tissue residue depletion study in pigs was submitted. The study was in accordance with current VICH guidance. Test animals were administered the active substance daily in medicated drinking water and received the recommended dose for the recommended duration. Suitable analysis was performed. Data supported a withdrawal period of 4 days.

MRLs

Fenbendazole is listed in Table 1 of Regulation 37/2010.
Maximum residue limits (MRLs) are listed below:

	All food-producing species except fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'
Marker residue: Sum of extractable residues which may be oxidised	
Muscle	50 µg/kg
Liver	500 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	10 µg/kg
Eggs	1300 µg/kg

Withdrawal Periods

Meat and offal: 4 days.
[1] CVMP – Committee for Medicinal Products for Veterinary Use.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance, as described in Section III.

Tolerance in the Target Species

A number of published references were submitted to support use of the product in the target species. In addition, a target animal safety study was submitted, which used the product at 1x, 3x and 5 x the recommended dose for 4.5 x the duration of treatment.

Resistance
Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation
Laboratory Trials
In addition to providing a series of data from published literature describing the use of fenbendazole in pigs, the applicant has conducted three pivotal dose determination and confirmation studies.

Dose confirmation studies:

(1) Study title	Evaluation of the efficacy of a proposed product, 200 mg/ml oral suspension against adult and larval stages of *Ascaris suum* in weaned pigs
Objectives	To evaluate the efficacy of a 200 mg/ml proposed product, containing fenbendazole, when administered in drinking water at a dose rate of 2.5 mg fenbendazole/kg/day for 2 consecutive days, against the adult, migrating larvae and intestinal larval stages of *Ascaris suum*.
Test site(s)	United Kingdom
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	200 mg/ml oral suspension containing fenbendazole
Control product/placebo	Non-medicated water
Animals	150 pigs from which 100 were selected for study. 6-7 weeks old, sex ratio 1:1. 5 days acclimatisation prior to study. Group-housed. Animals were included if healthy and helminth naïve. Excluded if diseased, previously exposed to an antiheminthic or positive for *Ascaris suum*.
Randomisation	Randomisation was performed based on sex and bodyweight.
Blinding	Blinding during the *in vivo* phase was not possible due to the appearance of the product when compared to the control. Personnel responsible for parasite count were unaware of the allocation of animals to groups.
Method	Initial clinical assessment, faecal samples

	were collected from all animals at appropriate time points. Animals were divided into 6 groups: 1. Adult control (20 animals) 2. Adult (20 animals) 3. Migrating larvae control (10 animals) 4. Migrating larvae (10 animals) 5. Intestinal larvae (20 animals) 6. Intestinal larvae (20 animals) Animals were inoculated with parasite eggs and subsequently treated for infection over a series of days, then necropsied at various time points. Product was administered via drinking water at a dose rate of 2.5 mg/kg/day for 2 days. Once the medicated product was consumed, the animals were offered non-medicated water.
Statistical method	The individual animal was considered as the experimental unit, relying on the assumption that animals within a pen were statistically independent of each other. The worm counts were log transformed prior to analysis using log(count + 1) in order to allow for zero counts. An analysis of variance was used to assess differences between treatment groups. The means from the log transformed data were back-transformed to give geometric means. The % reduction in parasite count was calculated as follows: % reduction = 100 x [(geometric mean of control group – geometric mean of treated group) / geometric mean of control group]

	The adequacy of parasite infection observed in control animals was assessed based on historical, parasitological and/or statistical criteria. With regard to the latter, the infection was deemed adequate if the lower 95% confidence limit for the geometric mean of the control group was greater than 10% of the geometric mean of that group.
RESULTS	In all cases, statistically significant differences equating to $p < 0.05$ was obtained.
DISCUSSION	The product is efficacious as stated in the SPC and product literature.

(2) Study title	Evaluation of the efficacy of a proposed product, 200 mg/ml oral suspension against the Ghent strain of *Ascaris suum* in weaned pigs
Objectives	To evaluate the efficacy of a 200 mg/ml proposed product, containing fenbendazole, when administered in drinking water at a dose rate of 2.5 mg fenbendazole/kg/day for 2 consecutive days against the Ghent strain of *Ascaris suum*
Test site(s)	United Kingdom
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	200 mg/ml oral suspension containing fenbendazole
Control product/placebo	Non-medicated water
Animals	150 pigs from which 40 were selected for study (plus two additional animals). 6-7 weeks old, sex ratio 1:1. 5 days acclimatisation prior to study. Group-housed. Animals were included if healthy and helminth naïve. Excluded if diseased, previously exposed to an antiheminthic or positive for *Ascaris suum*.
Randomisation	Randomisation was performed based on sex and bodyweight.
Blinding	Blinding during the *in vivo* phase was not possible due to the appearance of the

	product when compared to the control. Personnel responsible for parasite count were unaware of the allocation of animals to groups.
Method	Initial clinical assessment, faecal samples were collected from all animals at appropriate time points. Animals were divided into 2 groups: 1. Intestinal larvae control (20 animals) 2. Intestinal larvae (20 animals) Animals were inoculated with parasite eggs and subsequently treated for infection over a series of days, then necropsied at various time points. Product was administered via drinking water at a dose rate of 2.5 mg/kg/day for 2 days. Once the medicated product was consumed, the animals were offered non-medicated water.
Statistical method	The individual animal was considered as the experimental unit, relying on the assumption that animals within a pen were statistically independent of each other. The worm counts were log transformed prior to analysis using log(count + 1) in order to allow for zero counts. An analysis of variance was used to assess differences between treatment groups. The means from the log transformed data were back-transformed to give geometric means. The % reduction in parasite count was calculated as follows: % reduction = 100 x [(geometric mean of control group – geometric mean of treated group) / geometric mean of

	control group] The adequacy of parasite infection observed in control animals was assessed based on historical, parasitological and/or statistical criteria. With regard to the latter, the infection was deemed adequate if the lower 95% confidence limit for the geometric mean of the control group was greater than 10% of the geometric mean of that group.
RESULTS	In both cases, statistically significant differences equating to $p < 0.05$ was obtained.
DISCUSSION	The product is efficacious as stated in the SPC and product literature.

(3) Study title	Evaluation of the efficacy of a water soluble fenbendazole product against adult and migrating larval stages of *Ascaris suum* in weaned pigs
Objectives	To evaluate the efficacy of the proposed product under controlled conditions against adult and migrating larval stages of *Ascaris suum* in experimentally infected pigs, when administered at a dose of 2.5 mg/kg for 2 consecutive days.
Test site(s)	United Kingdom
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	200 mg/ml oral suspension containing fenbendazole
Control product/placebo	Non-medicated water
Animals	56 pigs 8-9 weeks old, male and female. 5 days acclimatisation prior to study. Group-housed after initial individual housing. Animals were included if healthy and helminth naïve. Excluded if in need of anti-parasitic, antibiotic or anti-inflammatory treatment other than the proposed product.
Randomisation	Randomisation was performed based on sex and bodyweight.

Blinding	Personnel responsible for necropsy and helminth enumeration were blinded to treatment.
Method	Initial clinical assessment, faecal samples were collected from all animals at appropriate time points. Animals were divided into 4 groups: 1. Adult control (20 animals) 2. Adult (20 animals) 3. larval control (8 animals) 4. larval (8 animals) Animals were inoculated with parasite eggs and subsequently treated for infection over a series of days, then necropsied at various time points. The methodology was administered appropriately within the groups to assess adulticidal and larvicidal efficacy of the product. Product was administered via drinking water at a dose rate of 2.5 mg/kg/day for 2 days. Once the medicated product was consumed, the animals were offered non-medicated water.
Statistical method	The primary efficacy criterion was the percentage reduction of worm count at necropsy for the treated groups compared to the control groups. In accordance with VICH GL7 (Efficacy of anthelmintics: general requirements), statistical analysis of the study was a two-stage procedure. Firstly, the mean worm burdens in the treated groups were compared to those in the corresponding control groups using the Mann-Whitney test. Differences between groups were considered significant when the p value was 0.05 or lower.

	Prior to further analysis, worm counts were log-transformed using log(count + 1). Percentage efficacy was subsequently determined using Abbott's formula, as follows: % Efficacy = ((C – T)/C) x 100 where C is the geometric mean of the control group and T is the geometric mean of the treated group. The percentage reductions in egg output on days 62, 63, 65 and 76 were also calculated using Abbott's formula. Differences in egg output between groups A and B on day 76 were statistically analysed using the Mann-Whitney test while differences in egg output between days 65 and 76 (for both groups A and B) were analysed using the Wilcoxon matched-pairs signed rank test.
RESULTS	In all cases, statistically significant differences equating to $p < 0.05$ was obtained. Mean efficacy was >90%.
DISCUSSION	The product is efficacious as stated in the SPC and product literature.

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(s) is favourable.