IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Pigfen 40 mg/g granules for pigs99

PRODUCT SUMMARY

EU Procedure number	IE/V/0596/001 (formerly UK/V/0550/002)
Name, strength and pharmaceutical form	Pigfen 40 mg/g granules for pigs
Active substances(s)	Fenbendazole
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Legal basis of application	Well-established use application (Article 13a of Directive No 2001/82/EC)
Date of Authorisation	17 June 2015 (UK) 11 September 2015 (IE)
Target species	Pigs
Indication for use	Treatment of pigs infected with *Ascaris suum* (adult, intestinal and migrating larval stages).
ATCvet code	QP52AC13
Concerned Member States	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Spain UK added via change of RMS

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

Pigfen 40 mg/g Granules for Pigs was submitted as a bibliographic application. The product contains fenbendazole and is indicated for the treatment of *Ascaris suum* (adult, intestinal and migrating larval stages) infections in pigs. The product is contraindicated where there is known hypersensitivity to the active substance, other benzimidazoles or any of the excipients. Pigs to be treated should be separated and treated individually.
The product may be administered to pigs using the following dosage regimens:

- Single dose of 5 mg fenbendazole (corresponding to 125 mg of the product) per kg bodyweight (migrating larval, intestinal larval and adult stages);
- 0.72 mg fenbendazole (corresponding to 18 mg of the product) per kg bodyweight per day for 7 consecutive days (intestinal larval and adult stages);
- 0.36 mg fenbendazole (corresponding to 9 mg of the product) per kg bodyweight per day for 14 consecutive days (intestinal larval and adult 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 as the active substance and the excipients maize starch and pregelatinised starch.

The container/closure system consists of polyethylene/ aluminium foil/ polyethylene terephthalate zipper bags containing 0.25 kg, 0.5 kg or 1 kg of product. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is 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 mixing the fenbendazole with the excipients until homogenised before granulation of the mix. Finally the mix is packaged into the zipper bags. 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.). A Ph. Eur. Certificate of Suitability was provided for the manufacturer of the active substance. 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 are manufactured in accordance with their respective monographs. Certificates of analysis were provided.

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

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. Control tests on the finished product include those for identification and assay of the active substance, identification of impurities, appearance, particle size and microbial quality.

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.

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 active substance is manufactured in accordance with a Ph. Eur. Certificate of Suitability and has a retest period of 2 years.

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 were provided for batches stored at 25ºC/60%RH and 30ºC/65%RH for up to 36 months, and at 40ºC/75%RH for up to 6 months. A shelf life of 2 years was supported.

In-use stability data were provided for batches opened and stored at 20 - 25ºC and 40 - 55%RH for 3 months. An in-use shelf life of 3 months was established.

G. Other Information
Shelf life of the finished product as packaged for sale is 2 years.
Shelf life after first opening the immediate packaging is 3 months.
Do not store above 25 ºC after first opening the immediate packaging.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation
Pharmacological Studies
Pharmacodynamics
Fenbendazole is part of the benzimidazole class of anthelmintics. Benzimidazole anthelmintics depolymerise microtubules and disrupt microtubule based processes in helminths. Fenbendazole is used to treat gastrointestinal (GI) parasite infections and has a broad spectrum of activity against GI nematodes. Fenbendazole can be administered as a single dose therapy or in divided doses administered over several days.

Pharmacokinetics
The CVMP established the absorption, distribution, metabolism and excretion of fenbendazole as part of the MRL process. Studies using radiolabelled fenbendazole have shown that absorption and excretion are slower in ruminants than monogastric animals. In ruminants, benzimidazoles are released from the rumen slowly, whereas in monogastric animal repeat doses are sometimes needed for optimal efficacy.

Fenbendazole is metabolised by the liver through oxidation, hydroxylation and degradation to form a series of other benzimidazoles, such as oxfendazole. Fenbendazole is primarily excreted through the faeces.

In a study in pigs, fenbendazole was absorbed rapidly following oral administration of a single 5 mg/kg dose. It was quickly metabolised. Fenbendazole was only detected for the first 2 hours after treatment whilst the metabolites reached a peak 8 hours after administration. Fenbendazole and the metabolites were non-detectable by 60 hours after administration.

Toxicological Studies
Fenbendazole is a well-established substance that has been widely and safely used for many years. Generally benzimidazoles are well tolerated in mammals and show a selective toxicity for helminths. Bibliographical data have been provided for toxicity.

- Single Dose Toxicity

Fenbendazole has low acute toxicity. LD_{50} values of >10,000 mg/kg have been recorded in rats and mice.

- Repeated Dose Toxicity

Repeat dose toxicity studies have been performed in rats and dogs. No adverse effects were observed in rats administered 2,500 mg/kg/day for 30 days, however tremors were noted in rats given 1,600 mg/kg/day orally for 90 days. In dogs the most common toxic effect was lymphoid hyperplasia following repeat doses for 6 days to 6 months. The NOEL[1] was 4 mg/kg/day in dogs.

- Reproductive Toxicity, including Teratogenicity:

A 3-generation study in rats produced an NOEL of 15 mg/kg/day. At doses of 45 mg/kg/day diarrhoea, reduced bodyweight and pathological changes in the liver were observed in parents. Reduced fertility, survival and growth of neonates during lactation was also observed.

No evidence of foetotoxicity and teratogenicity was seen in rats given doses of up to 2,500 mg/kg from day 7-16 of gestation. In rabbits given up to 63 mg/kg on days 7-19 of gestation delayed ossification was observed. The NOEL was found to be 25 mg/kg. The CVMP report no treatment related effects in offspring of dogs, pigs, sheep and cattle administered fenbendazole during gestation; and no effect in testicular function in sheep and horses.

- Mutagenicity

A number of mutagenicity tests have been performed and produced negative results. There is no evidence of genotoxicity.

- Carcinogenicity

No evidence of carcinogenicity was seen in mice administered 405 mg/kg fenbendazole for up to 2 years. In rats given dietary doses of 135 mg/kg fenbendazole, reduced bodyweight gain and survival rates were seen. Histological changes were seen in the liver; the NOEL was determined as 5 mg/kg/day.

Observations in Humans
Fenbendazole is not used in human medicine. A study evaluating the pharmacokinetics and tolerability in humans was reported. No effects were seen in subjects given oral doses of 300 mg or 600 mg fenbendazole.

User Safety
A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure are dermal and ocular or inhalation due to the dust. The product will be administered by professionals and the risk to the user is considered to be low. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- This product may cause eye irritation and skin sensitisation.
- Avoid contact with skin and/or eyes.
- When handling or mixing, care should be taken to avoid direct contact with the skin and eyes, and inhalation of dust, by wearing goggles, impervious gloves and a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.
- Wash hands after use.
- In case of skin and/or eye contact, immediately rinse with plenty of water.

Environmental Safety
An Environmental Risk Assessment (ERA) was provided. The ERA was performed in accordance with VICH and CVMP guidelines.

Phase I:
The product will be administered to pigs at a dose rate of 5 mg/kg to treat *Ascaris suum* infections. Fenbendazole has the potential to be released to the environment by spreading the slurry on agricultural land. The predicted environmental concentration (PEC) in soil was calculated and it was assumed that 100% of the herd had been treated. The PEC_{soil} was less than 100 µg/kg. Therefore, a Phase II ERA was not required.

III.B.2 Residues documentation
Residue Studies
A residue depletion study using the final formulation has been conducted in pigs. Samples of kidney, liver, muscles and skin/fat were taken from animals at several time points. Results show that residues depleted to below the MRL, in all tissues, before the end of the withdrawal period. Statistical analysis of the results was used to set the withdrawal period.

The analytical method was GLP-compliant, using ultra-performance liquid chromatography and mass spectrometry. The method was fully validated.

MRLs
MRLs have been established for fenbendazole in edible tissues. The marker residue is the sum of fenbendazole and its metabolites, oxfendazole and oxfendazole sulphone. The excipients are included in the out of scope list.

MRLs are listed below:

	Pig
Muscle	50 µg/kg
Liver	500 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg

Withdrawal Periods
Based on the data provided, the below withdrawal period is justified.
Meat and offal: 4 days
[1] NOEL – No observable effect level

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies
Pharmacology
Pharmacodynamics
Fenbendazole is part of the benzimidazole class of anthelmintics. Benzimidazole anthelmintics depolymerise microtubules and disrupt microtubule based processes in helminths. Fenbendazole is used to treat gastrointestinal (GI) parasite infections and has a broad spectrum of activity against GI nematodes. Fenbendazole can be administered as a single dose therapy or in divided doses administered over several days.

Pharmacokinetics
The CVMP established the absorption, distribution, metabolism and excretion of fenbendazole as part of the MRL process. Studies using radiolabelled fenbendazole have shown that absorption and excretion are slower in ruminants than monogastric animals. In ruminants, benzimidazoles are released from the rumen slowly, whereas in monogastric animal repeat doses are sometimes needed for optimal efficacy.

Fenbendazole is metabolised by the liver through oxidation, hydroxylation and degradation to form a series of other benzimidazoles, such as oxfendazole. Fenbendazole is primarily excreted through the faeces.

In a study in pigs, fenbendazole was absorbed rapidly following oral administration of a single 5 mg/kg dose. It was quickly metabolised. Fenbendazole was only detected for the first 2 hours after treatment whilst the metabolites reached a peak 8 hours after administration. Fenbendazole and the metabolites were non-detectable by 60 hours after administration.

Tolerance in the Target Species

A controlled target animal tolerance study using multiples of the recommended dose in the target species has been provided. The study was GLP-compliant. The test product was administered to pigs orally for 3 consecutive days at 1x, 3x and 5x normal dose. A negative control was used. Animals were randomly assigned to a test group and no animals had received a benzimidazole anthelmintic 14 days before the study.

Parameters considered were mortality, bodyweight, clinical observations, feed intake, water intake and blood samples. No adverse effects were seen following doses up to 5 times the recommended dose.

Resistance
Information has been provided on anthelmintic resistance in pigs. The literature showed that resistance has been identified to levamisole, piperazine and thiabendazole in *Oesophagostomum* spp. and *Trichuris suis*. The status of fenbendazole resistance in *A. suum* appears to be unknown at the time of authorisation but the risk of resistance developing cannot be excluded. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation
Laboratory Trials
A dose confirmation study has been provided, along with bibliographical data which show that fenbendazole has been found to be efficacious against roundworms, nodular worms, stomach worms, whipworms and lungworms in pigs. Specifically, literature references were provided in support of the efficacy of fenbendazole administered as a divided dose against *A. suum*.

In one study crossbred pigs were given third-stage *A. suum* larvae via oral administration. On days 8, 9 and 10 half the pigs were dosed with 3 mg/kg/day fenbendazole in the feed. The other half were untreated and formed the control group. Five days after treatment the pigs were necropsied and worm counts were performed. Worms were not found in treated pigs but a total of 109 worms were found in the control group.

In another study, 96 crossbred pigs were orally administered embryonated eggs of *A. suus*, *T. suis* and third stage larvae of *Oesophagostomum dentatum* daily for 3 consecutive days. Following a 10 day incubation period pigs were assigned to 1 of 4

groups. Three groups were treated with an anthelmintic and one group was untreated (control). The treatments were either dichlorvos, ivermectin or 3 mg/kg/day fenbendazole administered orally over 3 consecutive days. After 47 days half the pigs from each group were necropsied and worms were counted. Efficacy for each species was calculated by comparing the treated groups with the control group. Faecal egg counts (FEC) were used to monitor efficacy in the remaining pigs.

The results showed that following treatment with fenbendazole the percentage of pigs with a positive worm count was 0% compared with 83.3% of the control group. Based on this 100% efficacy of fenbendazole against *A. suum* was calculated. The FEC data were also compared between the control and fenbendazole treated groups. The percentage of FEC positive pigs following treatment was 0% compared to 77.8% in the control group. It was concluded that fenbendazole is effective against *A. suum*.

Dose confirmation studies:

Study title	Study to evaluate the efficacy of fenbendazole against adult *Ascaris suum* in weaned pigs
Objectives	To evaluate the efficacy of the test product under controlled conditions against adult worms of *Ascaris suum* in experimentally infected pigs.
Test site(s)	Single-centre, EU.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 40 mg/g Single dose of 5 mg/kg BW
Control	Negative control
Animals	40 commercial hybrid pigs, male and female, aged between 8-9 weeks, weighing 15-24 kg. The animals were clinically healthy and essentially helminth naïve.
Outcomes/endpoints	Primary end point was the % reduction in worm count. The % efficacy was then calculated from this.
Randomisation	Randomised.
Blinding	Single blind.
Method	Animals were divided into treatment groups on day -7 and had a 6 day acclimatisation period. On day -1, 0 and 1 pigs were experimentally infected with embryonated eggs of *A. suum*. On day 45 pigs from the treatment group were individually dosed with the test product mixed in 20% of the daily feed ration. On days 45, 47, 49 and 51 faecal samples were collected from all pigs and egg counts were performed using the McMaster method. The sensitivity used was 50 eggs per gram (epg). Daily observations were also made and any clinical signs recorded. On day 52 animals were necropsied and worm counts were performed.
Statistical method	A two-sided sample t-test was used to compare the mean worm burden of the two groups. Differences were considered significant at $p \leq 0.05$.
RESULTS	
Outcomes for endpoints	The mean number of worms by day 51 was 49.85 in the control group and 1 in the treatment group ($p < 0.01$). The % efficacy was calculated as 99.9%. The mean egg counts were also calculated for the control and treatment groups. The mean decreased following treatment and continued to rise until day 51 for the control animals. The% reduction was found to be 85.8% ($p < 0.05$).
DISCUSSION	It was concluded that the test product is efficacious against *A. suum* in pigs infected experimentally.

Study title	Study to evaluate the efficacy of fenbendazole against adult and larval stages of *Ascaris suum* in weaned pigs.
Objectives	To evaluate the efficacy of the test product under controlled conditions against the adult and larval stages of the swine helminth *Ascaris suum* in experimentally infected pigs if administered as a single dose of 5 mg/kg or as the same dose divided over 7 days (0.71 mg/kg).
Test site(s)	Single-centre, EU.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 40 mg/g Either a single dose of 5 mg/kg BW or 0.71 mg/kg BW for 7 consecutive days.
Control	Negative control
Animals	84 commercial hybrid pigs, male and female, aged between 8-9 weeks, weighing 13-20 kg. The animals were clinically healthy and essentially helminth naïve.
Outcomes/endpoints	Primary end point was the % reduction in worm count. The % efficacy was then calculated from this.
Randomisation	Randomised.
Blinding	Single blind.
Method	Animals were divided into treatment groups: A – infected with adult worms and untreated B – infected with adult worms and single dose C - infected with adult worms and daily dosing D – infected with larvae and untreated E – infected with larvae and single dose F – infected with larvae and daily dosing The animals had a 7 day acclimatisation period. On day 0 the animals were inoculated with *A. suum eggs*. Groups A-C Faecal examination to determine epg was performed on day 50 and Group C began treatment. On day 56 Group B pigs were treated and faecal examination for all groups. On day 64 the animals were necropsied for worm and egg counts. FEC were performed using the McMaster method (sensitivity: 50 epg). Groups D-F Group F started treatment on day 2, ending on day 8. On day 8 Group E received the treatment. On day 14 animals were necropsied for worm counts.
Statistical method	A two-sided sample t-test was used to compare the mean worm burden of the two groups. Differences were considered significant at $p \leq 0.05$.
RESULTS	
Outcomes for endpoints	<u>Larval stage</u> The mean number of worms identified was 45 in Group D, 0.25 in Group E and 0 in Group F. The difference between Group D and Group E was significant ($p < 0.01$), as was the difference between Group D and Group F ($p < 0.01$). The efficacy was calculated as 99.4% for single dose treatment and 100% for daily dosing for 7 days.

	Adult stage The mean number of worms identified was 2.74 in Group A, 0 in Group B and 0 in Group C. The differences in the number of worms between Group A and B, and Group A and C were significant ($p < 0.05$). The efficacy was calculated as 100% for both dosing regimes. The percentage reduction in egg counts was compared following treatment. The reduction for Group B was 95.07% and for Group C was 100%.
DISCUSSION	It was concluded that the test product is effective at reducing the number of adults and larvae of *A. suum* in experimentally infected pigs.

Field Trials

As this application was made in accordance with Article 13a of Directive 2001/82/EC as amended, and the use of the active substance in veterinary medicine is well established, field studies were 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 of the product(s) is favourable