Veterinary Medicines Directorate

**United Kingdom**
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**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Pigfen 40 mg/g Premix for Medicated Feeding Stuff for Pigs

**Date Created: December 2016**

**PuAR correct as of 14/01/2019 when RMS was transferred to IE. Please contact the RMS for future updates.**

# MODULE 1

## PRODUCT SUMMARY

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|---|---|
| EU Procedure number | UK/V/0600/001/DC |
| Name, strength and pharmaceutical form | Pigfen 40 mg/g Premix for Medicated Feeding Stuff for Pigs |
| Applicant | Huvepharma N.V.<br>Uitbreidingstraat 80<br>Antwerpen<br>B-2600<br>Belgium |
| Active substance(s) | Fenbendazole |
| ATC Vetcode | QP52AC13 |
| Target species | Pigs |
| Indication for use | Treatment of pigs infected with *Ascaris suum* (adult, intestinal and migrating larval stages) susceptible to fenbendazole. |

# 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

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|---|---|
| Legal basis of original application | Generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended |
| Date of completion of the original decentralised procedure | 21 September 2016 |
| Date product first authorised in the Reference Member State (MRP only) | Not applicable |
| Concerned Member States for original procedure | Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Slovakia, Spain |

## I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid' application submitted in accordance with Article 13 (3) of Directive 2001/82/EC (as amended) because bioequivalence could not be demonstrated with the reference product. The reference product is Panacur 4% Powder Premix for Medicated Feed which has been marketed in the UK since 1994.

The product is indicated for the treatment of pigs infected with *A. suum* (adult, intestinal and migrating larval stages) susceptible to fenbendazole.

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.[1] 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 [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 CONSTIUENTS

## *II.A. Composition*

The product contains 40 mg fenbendazole and excipients maize starch and pregelatinised starch.

The container/closure system consists of a multiple-layer paper bag with internal aluminium/polyethylene layer for the 20 kg presentation and polyethylene/aluminium foil/polyethylene terephthalate zipper bag for the 1, 2 and 5 kg presentations. 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 simple mixing and filling process.

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 substance described in the European Pharmacopoeia. 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.

Fenbendazole is supplied in accordance with a valid Certificate of Suitability.

The excipients, pregelatinised starch and maize starch, are described in the European Pharmacopoeia.

## *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 three 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. 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: appearance, colour, particle size, microbiological quality, identification and content of fenbendazole.

### *II.F. Stability*

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. Batches were stored under VICH[3] conditions of 25°C/60% RH and 40oC/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

### *G. Other Information*

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

Shelf life after first opening the immediate packaging: 3 months.

Shelf life after incorporation into meal or pelleted feed: 3 months.

This veterinary medicinal product does not require any special storage conditions.

## III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic ‘hybrid’ application according to Article 13 (3) and bioequivalence with a reference product has not been demonstrated. The maximum residues limit (MRL) summary report for fenbendazole and review references in support of the pharmacological and toxicological data requirements were provided.

[3] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

## *III.A Safety Documentation*

### *Pharmacological Studies*

Bibliographical data has been provided which show that fenbendazole is an anthelmintic belonging to the benzimidazole-carbamate group. It acts by binding to beta-tubulin, thereby inhibiting the polymerisation of tubulin to microtubules and subsequently interfering with energy metabolism. The anthelmintic affects both adult and immature stages of *A. suum*.

The applicant has also has provided bibliographical data which show that fenbendazole is only partly absorbed after oral administration and is then metabolised in the liver. Fenbendazole and its metabolites are distributed throughout the body and high concentrations can be found in the liver. The elimination of fenbendazole and its metabolites occurs primarily via the faeces (>90%) and to a small extent in the urine and milk. Fenbendazole is metabolised to its sulphoxide, then to sulphone and amines.

### *Toxicological Studies*

The applicant has provided the CVMP[4] MRL summary report which shows:

- Single Dose Toxicity

Fenbendazole is of low acute toxicity, with oral $LD_{50}$ values >10 000 mg/kg in rats and mice.

- Repeated Dose Toxicity

Repeat dose toxicity studies have been conducted in rats and dogs. No adverse effects were seen in rats given fenbendazole orally at doses up to 2500 mg/kg/day for 30 days. However, in a 90 day study, tremors were observed in groups of rats receiving a dose of 1600 mg/kg or higher.

In other repeat dose studies, dogs were administered oral gelatin capsules daily for between 6 days to 6 months. The main toxic effect was lymphoid hyperplasia in the gastric mucosa and mesenteric lymph nodes. The overall no observed effect level (NOEL) was 4 mg/kg bodyweight (bw)/day based on lymphoid hyperplasia observed in dogs.

- Reproductive Toxicity, including Teratogenicity:

In a 3-generation study in rats with fenbendazole administered in the diet, parental animals presented with diarrhoea, reduced bodyweight gain and pathological changes in the liver at doses of over 45 mg/kg. At the same dose rates, there was reduced fertility, survival and growth of the neonates during lactation. The NOEL was 15 mg/kg per day.

Fenbendazole failed to induce any adverse effects against reproduction in male and female animals at doses of up to 15 mg/kg bw/day, without inducing

[4] The Committee for Medicinal Products for Veterinary Use

systemic toxicity. Fenbendazole was devoid of any teratogenic properties in a number of species, including rats, dogs, cattle and sheep. In the most sensitive species, the rabbit, a NOEL of 25 mg/kg bw/day was established.

- Mutagenicity

Fenbendazole was negative in a number of mutagenicity tests. The only test that gave positive results was the mouse lymphoma forward mutation assay in the presence of metabolic activation. However, it is agreed that no clear evidence of genotoxicity has been shown.

- Carcinogenicity

Studies in mice and rats showed effects on survival at the high dose rate. In rats bodyweight gain was affected at 45 and 135 mg/kg. Histological changes were seen primarily in the liver including hepatocellular hypertrophy, hyperplasia and vacuolation, bile duct proliferation and biliary cyst formation. The overall NOEL was 5 mg/kg.

### *Observations in Humans*

Fenbendazole is not used in human medicine. However in a tolerability study, male subjects were given a dose of 300 mg fenbendazole with breakfast, or 600 mg 12 hours after their last meal. The men showed no relevant changes in blood pressure, pulse rate, symptom list, self-rating scale or clinical chemistry.

### *User Safety*

A user risk assessment was provided in compliance with the relevant guideline which shows:

This product may cause eye irritation.

The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- 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.
- Do not eat or smoke during handling the premix or the medicated feed.

### *Environmental Safety*

**Phase I:**
A Phase I Environmental Risk Assessment (ERA) has been submitted and conducted in accordance with VICH and CVMP Guidance. The VICH decision tree has been followed to reach a stop based on the PEC values in soil being less than 100 µg/kg (question 17). All the $PEC_{soil}$ calculations for a range of usage scenarios in pigs were estimated and were shown to be below the trigger threshold of 100 µg/kg. Therefore a Phase II assessment is not required and the risk to the environment from use of the product is considered acceptable. The inclusion of environmental warnings for aquatic organisms in sections 4.5.iii and 6.6 of the SPC are supported.

## *III.B.2 Residues documentation*

### *Residue Studies*

The applicant conducted a GLP[5] compliant residue depletion study which showed that the withdrawal period of 4 days for meat and offal as stated in the SPC is adequate.

### *MRLs*

Fenbendazole is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk. The marker residue is the sum of fenbendazole, oxfendazole and oxfendazole oxidised to the common oxide (fenbendazole sulfone).

MRLs are listed below:

| Pharmacologically active substance(s) | Marker residue | Animal species | MRLs (µg/kg) | Target tissues | Other provisions |
|---|---|---|---|---|---|
| Fenbendazole | Sum of extractable residues which may be oxidised to fenbendazole sulfone | All ruminants, porcine, equidae | 50 µg/kg<br>50 µg/kg<br>500 µg/kg<br>50 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | For porcine species the fat MRL relates to 'skin and fat in natural proportions' |
| | | All ruminants | 10 µg/kg | Milk | |

### *Withdrawal Periods*

Based on the data provided, the withdrawal period of four days for meat and offal are justified.

[5] Good Laboratory Practice

# IV CLINICAL DOCUMENTATION

This is a generic hybrid application according to Article 13 (3) and bioequivalence with a reference product was not demonstrated, therefore published literature was provided to support the pharmacodynamics, pharmacokinetics, resistance status and target animal safety of the active substance. In addition, to provide data relating to the final formulation, the applicant has conducted a target animal safety study and two dose confirmation studies in which the efficacy of Pigfen 40 mg/g Premix for Medicated Feeding Stuff against *A. suum* infestation was determined.

## *IV.I. Pre-Clinical Studies*

### *Pharmacology*

Bibliographical data has been provided which show that fenbendazole is an anthelmintic belonging to the benzimidazole-carbamate group. It acts by binding to beta-tubulin, thereby inhibiting the polymerisation of tubulin to microtubules and subsequently interfering with energy metabolism. The anthelmintic affects both adult and immature stages of *A. suum*.

The applicant has also has provided bibliographical data which show that fenbendazole is only partly absorbed after oral administration and is then metabolised in the liver. Fenbendazole and its metabolites are distributed throughout the body and high concentrations can be found in the liver. The elimination of fenbendazole and its metabolites occurs primarily via the faeces (>90%) and to a small extent in the urine and milk. Fenbendazole is metabolised to its sulphoxide, then to sulphone and amines.

### *Tolerance in the Target Species*

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species. No treatment was used as a control. All doses were administered by sprinkling on top of feed on 3 occasions. Parameters evaluated were mortality, bodyweight, clinical observations, general physical observations, feed and water consumption and blood samples. No adverse effects were seen following doses up to five times the recommended dose.

Bibliographical data have also been provided which shows that doses of >400 times the proposed dose resulted in leukopaenia and increased levels of sorbitol dehydrogenase, which were reversible. Doses of 25 times the proposed dose were generally well tolerated. The literature supported the study findings that there were no abnormal findings when sows were given up to five times the dose stated for the proposed product for five consecutive days. The data provided demonstrates a wide safety margin for fenbendazole in pigs.

### *Resistance*

The bibliography provided suggests that there is limited data available regarding the development of resistance to fenbendazole in *A. suum* in pigs. As there is a lack of evidence the risk of resistance development cannot be excluded therefore adequate warnings and precautions appear on the product literature.

## *IV.II. Clinical Documentation*

### *Laboratory Trials*

The applicant has conducted a number dose confirmation studies to support a single dose or 7 or 14 day treatment program.

### *Dose confirmation studies:*

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| Study title | Study to evaluate the efficacy of fenbendazole against adult *Ascaris suum* in weaned pigs |
| Objectives | To evaluate the efficacy of the proposed product (fenbendazole 40 mg/g oral granules) under controlled conditions against adult worms of *A. suum* in experimentally infected pigs. |
| Test site(s) | Single site. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fenbendazole 40 mg/g oral granules. Administered with feed, once. |
| Control | No treatment |
| Animals | 40 pigs (female and castrated males), approx. 8-9 weeks old, 15-24 kg bodyweight.<br>Inclusion Criteria<br>Helminth naïve<br>Clinically healthy<br>Exclusion Criteria<br>Unhealthy animals |
| Outcomes/endpoints | Reduction in worm count and egg count. |
| Randomisation | Randomised. |
| Blinding | Blinded. |
| Method | Acclimatisation period (six days)<br>Animals experimentally infected with *A. Suum*<br>Bodyweight was monitored and treatment with Fenbendazole 40 mg/g oral granules was given.<br>Post treatment clinical observations were recorded daily and faecal samples were taken at four specific time points. |
| Statistical method | Test the difference statistical tests were used to compare the differences in worm count and egg output between the two study groups.<br>Differences between groups were considered significant when $p \leq 0.05$. |

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| RESULTS | |
| Outcomes for endpoints | Worm Count – efficacy was >99%. There was a significant difference ($p < 0.01$) between the number of worms recovered from the two study groups.<br>Egg Output – efficacy was >85%. There was a significant difference ($p < 0.05$) in egg per gram values between the two study groups.<br>No significant adverse events were reported. |
| DISCUSSION | Fenbendazole 40 mg/g oral granules administered as a single 5 mg/kg dose was efficacious in reducing the number of *A. suum* adult worms in experimentally infected pigs. |

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| Study title | Study to evaluate the efficacy of fenbendazole against adult *Ascaris suum* in weaned pigs |
| Objectives | To evaluate the efficacy of the proposed product (fenbendazole 40 mg/g oral granules) under controlled conditions against the adult and larval stages of the swine helminth *A. 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 site. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fenbendazole 40 mg/g oral granules. Administered in feed either once or for seven consecutive days. |
| Control | No treatment |
| Animals | 84 pigs (female and castrated males), approx. 8-9 weeks old, 13-20 kg bodyweight.<br><u>Inclusion Criteria</u><br>Helminth naïve<br>Clinically healthy<br><u>Exclusion Criteria</u><br>Unhealthy animals |
| Outcomes/endpoints | Reduction in worm counts (adult and larval stages) and egg output. |
| Randomisation | Randomised. |
| Blinding | Blinded. |
| Method | Acclimatisation period (seven days)<br>Animals experimentally infected with *A. Suum*<br>Bodyweight was monitored and treatment with Fenbendazole 40 mg/g oral granules was given.<br>Post treatment clinical observations were recorded daily and faecal samples were taken at three specific time points. |
| Statistical method | Test the difference statistical tests were used to compare the differences in worm count and egg output between the study groups.<br>Differences between groups were considered significant when $p \leq 0.05$. |

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| RESULTS | |
| Outcomes for endpoints | Larval Stage – efficacy was >99%. There was a significant difference (p = 0.01) between the number of worms recovered from the study groups.<br>Adult Stage – efficacy was 100% the results were not statistically significant (p = 0.05).<br>Egg Output – reduction was >85% for the single dose and 100% for the seven day treatment.<br>No significant adverse events were reported. |
| DISCUSSION | Fenbendazole administered as a single 5 mg/kg dose was efficacious in reducing the number of adults and larvae of *A. suum* in experimentally infected pigs. Fenbendazole administered for 7 consecutive days was efficacious in reducing the burden of larval and adult worms. The use of Fenbendazole granules appeared to be safe when the product was administered using these dosage regimens. |

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| Study title | Evaluation of the efficacy of fenbendazole in feed against adult and larval stages of *A. suum* in weaned pigs. |
| Objectives | To evaluate the efficacy of the proposed product Pigfen 40mg/g premix for medicated feeding stuff for pigs under controlled conditions against the adult, migrating larval and intestinal larval stages of the swine helminth *A. suum*, if administered in feed as a single dose, or as a divided dose over seven or 14 consecutive days totalling 5 mg/kg body weight. |
| Test site(s) | Single site (UK) |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Pigfen 40mg/g premix for medicated feeding stuff for pigs, administered in feed as a single dose, or as a divided dose over seven or 14 consecutive days totalling 5 mg/kg body weight. |
| Control product/placebo | No Treatment |
| Animals | 250 pigs, 1:1 ratio male:female, age 6-8 weeks on the day of parasite challenge. |
| Outcomes/endpoints | Reduction in worm counts (adult and larval stages) |
| Randomisation | Randomised |
| Blinding | Blinded. |
| Method | Faecal samples taken prior to infection.<br>Animals experimentally infected with *A. suum.*<br>Health check twice a day.<br>Necropsy to assess efficacy of proposed product. |
| Statistical method | Percentage reduction of parasitic burden. |
| RESULTS | |
| Outcomes for endpoints | Migratory larval stage – efficacy >99%<br>Intestinal larval stage – efficacy 100% |

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| | Adult stage – efficacy >95% |
| Adverse events | No significant adverse events were reported. |
| DISCUSSION | All treatment regimens tested in the study have shown the proposed product to be efficacious when administered at 5 mg/kg BW, over 1, 7 or 14 days, against adult and developmental stages of *A. suum*. |

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| Study title | Study to evaluate the efficacy of Pigfen 40 mg/g premix against adult and larval stages of *Ascaris suum* in weaned pigs. |
| Objectives | To evaluate the efficacy of the proposed product Pigfen 40 mg/g premix under controlled conditions against the adult and larval stages of the swine helminth *A. suum* in experimentally infected pigs (induced infection), if administered as a single dose of 5 mg/kg BW or as the same dose divided over 7 and 14 days. |
| Test site(s) | Single site (EU) |
| Compliance with Regulatory guidelines | Followed principles of Good Clinical Practice (GCP) |
| Test Product | Fenbendazole oral granules premix (40 mg/g) administered as a single dose or over 7 or 14 days at a total dose of 5 mg/kg bw |
| Control product/placebo | No Treatment |
| Animals | 140 pigs, females and castrated males, approx. 8 9 weeks old, weighing 13 - 20 kg. Helminth naïve and none had been treated prior to the study with anthelmintics. The pigs were acclimatised to study conditions for seven days.<br>Animals that were helminth naïve and clinically healthy with a normal appetite on day -7 were suitable for enrolment. |
| Outcomes/endpoints | Reduction in worm counts (adult and larval stages) |
| Randomisation | Randomised |
| Blinding | Blinded. |
| Method | Faecal samples taken prior to infection.<br>Animals experimentally infected with *A. suum.*<br>Health check twice a day.<br>Necropsy and egg counts to assess efficacy of proposed product. |
| Statistical method | Test the difference statistical tests were used to compare the differences in worm count between the study groups.<br>Results were reported as % efficacy |
| RESULTS | |
| Outcomes for endpoints | Migratory larval stage – efficacy >83%<br>Intestinal larval stage – efficacy >50%<br>Adult stage – efficacy >99% |
| Adverse events | No adverse events occurred. |
| DISCUSSION | Pigfen 40 mg/g premix administered at a dose of 5 |

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| | mg/kg divided over 7 and 14 days was very efficacious in the treatment of an infection with adult A. suum worms, with 100 % and 99.8 % reduction in worm counts respectively. The efficacy of both dose regimes was further supported by the significant reductions in faecal egg counts following treatment<br><br>The efficacy of a single dose of 5 mg/kg BW proved to be highly efficacious against the migratory larval stage of *A. suum* with a significant reduction in worm counts of 94.7 %. The same dose divided over 7 days also had a significant effect on the migratory larvae, with a reduction in worm counts of 84.4 %.<br><br>The efficacy of the proposed product, administered as a single dose and a 7-day treatment, against the intestinal larval stages could not be accurately measured as the infection levels in the untreated control animals was not adequate.<br><br>Finally, the use of the proposed product appeared to be safe for the animals when used in the administered dose levels and administration scheme. |

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| Study title | Evaluation of the efficacy of Pigfen 40 mg/g premix for medicated feeding stuff for pigs against a Ghent strain of *Ascaris suum* at the larval stage in weaned pigs. |
| Objectives | To evaluate the efficacy of the proposed product Pigfen 40mg/g premix for medicated feeding stuff for pigs under controlled conditions against the intestinal larval stages of the swine helminth *A. suum* from Ghent University, if administered in feed as a divided dose over 14 consecutive days totalling 5 mg/kg body weight. |
| Test site(s) | Single site (UK) |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Pigfen 40mg/g premix administered over 14 days at a dose rate of 0.36 mg/kg bw/day.<br>Animals needed to be helminth naïve, clinically healthy and aged approximately 6-8 weeks on the day of challenge. |
| Control product/placebo | No Treatment |
| Animals | 40 pigs, 1:1 ration male:female, age 6-8 weeks on the day of parasite challenge. The pigs were acclimatised to study conditions for a minimum of five days. |
| Outcomes/endpoints | Reduction in worm counts (larval stages) |
| Randomisation | Randomised |
| Blinding | Blinded. |
| Method | Faecal samples taken prior to infection. |

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| | Animals experimentally infected with *A. suum.*<br>Health check.<br>Necropsy and egg counts to assess efficacy of proposed product. |
| Statistical method | Non - parametric statistical tests were used to compare the differences in egg count between the study groups. |
| RESULTS | |
| Outcomes for endpoints | Efficacy against L4 intestinal larvae was not calculated by the applicant. However, it can be seen from the results that efficacy was 100%. |
| Adverse events | No adverse events occurred. |
| DISCUSSION | Pigfen 40mgig premix for medicated feeding stuff for pigs has been shown to be efficacious against *A. suum* intestinal larvae when administered at 0.36 mg/kg BW over 14 consecutive days. |

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| Study title | Evaluation of the efficacy of Pigfen 40mg/g premix for medicated feeding stuff for pigs against two strains of *Ascaris suum* at the migrating larval stage in weaned pigs. |
| Objectives | To evaluate the efficacy of the proposed product Pigfen 40mg/g premix for medicated feeding stuff for pigs under controlled conditions against the migrating larval stages of the swine helminth *A. suum,* when administered in feed as a divided dose over 14 consecutive days totalling 5 mg/kg body weight. |
| Test site(s) | Single site (UK) |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Pigfen 40mg/g premix administered over 14 days at a dose rate of 0.36 mg/kg bw/day.<br>Animals needed to be helminth naïve, clinically healthy and aged approximately 6-8 weeks on the day of challenge. |
| Control product/placebo | No Treatment |
| Animals | 80 pigs, 1:1 ration male:female, age 6-8 weeks on the day of parasite challenge. The pigs were acclimatised to study conditions for a minimum of five days. |
| Outcomes/endpoints | Reduction in worm counts. |
| Randomisation | Randomised |
| Blinding | Blinded. |
| Method | Faecal samples taken prior to infection.<br>Animals experimentally infected with *A. suum.*<br>Health check.<br>Necropsy and egg counts to assess efficacy of proposed product. |
| Statistical method | The primary efficacy criterion was the percentage larval worm count reduction at necropsy for the treated groups compared to the corresponding negative control groups. |

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| RESULTS | | |
| Outcomes for endpoints | Migratory larval stage | L4 efficacy >89%<br>L5 efficacy >100% |
| Adverse events | No significant adverse events occurred. | |
| DISCUSSION | The treatment regimen was efficacious against Ghent strain L4 and L5 stage *A. suum*. The L4 and L5 counts were totalled and the analysis showed an 99.3% reduction in *A. suum* from one strain, and a 100% reduction from the other and both analysis were highly significant (p-value = <0.001). This provides further support to the efficacy of the treatment regimen with Pigfen 40mg/g premix for medicated feeding stuff for pigs against both the Ghent and the UK strains. | |

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| Study title | Evaluation of the efficacy of fenbendazole in feed against migrating larval stages of *Ascaris suum* in weaned pigs. |
| Objectives | To evaluate the efficacy of the proposed product fenbendazole under controlled conditions against the migrating larval stage of the swine helminth *A. suum*, if administered in feed as two dose levels divided over seven consecutive days totalling 2.5 mg/kg body weight (BW) and 5 mg/kg BW. |
| Test site(s) | Single site (UK) |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Pigfen 40mg/g premix administered in feed as a single dose, or as a divided dose over seven or 14 consecutive days totalling 2.5 mg/kg bw or 5 mg/kg bw. |
| Control product/placebo | No Treatment |
| Animals | 40 pigs, 1:1 ratio male:female, age 6-7 weeks on the day of parasite challenge.<br>Animals needed to be helminth naïve and clinically healthy on the day of challenge. |
| Outcomes/endpoints | Reduction in worm counts (adult and larval stages) |
| Randomisation | Randomised |
| Blinding | Blinded. |
| Method | Faecal samples taken prior to infection.<br>Animals experimentally infected with *A. suum.*<br>Health check twice a day.<br>Necropsy to assess efficacy of proposed product. |
| Statistical method | 95% confidence limits were calculated for the geometric means and the adequacy of infection was based on assessing whether the lower confidence interval in the control group exceeded 10% of the geometric mean. Percentage efficacy was calculated as the percentage reduction of the treated group versus the control. |
| RESULTS | |
| Outcomes for | This is the first study to examine the lungs directly. The |

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| endpoints | results indicate that efficacy against migrating larvae was below the threshold of 90% stated in VICH GL16 for both the 0.36 mg/kg and 0.72 mg/kg dose (22.2% and 24.6, respectively. For the only 0.36 mg/kg group which was dosed correctly no efficacy was demonstrated (-3.1%). Efficacy above the 90% threshold was only demonstrated for the 0.72 mg/kg dose once the larvae had moved to the intestines as L4 larvae (97.6%). |
| Adverse events | No significant adverse events were reported. |
| DISCUSSION | The data, its analyses and interpretation successfully address the two aims within the study design. Firstly the results confirm the efficacy (97.6% based on the geometric mean) of a 7 day treatment (0.72mg/kg BW of fenbendazole) against the migrating stages of *A. suum* (7 days of treatment beginning on the third day after worm challenge). Secondly the results disproved the hypothesis that the efficacy of treatment of a new infection with *A. suum* relies solely on exposure of the larvae to anthelmintic once they have returned to the intestine following the migratory phase. To this effect the study investigated whether there was any effect after 7 days of treatment at 0.36 mg/kg BW of fenbendazole against migrating stages. The results here indicated that there was on average, per pig, more worms (from lung and small intestine) in control group pigs compared to the 0.36 mg/kg BW of fenbendazole treated pigs, although the results appear to not be statistically significant. |

The following administration advice is included in the SPC which reflects the result of the studies described above.

May be administered to pigs either as a single dose of 5 mg/kg (migrating larval, intestinal larval and adult stages) or by divided dose of 0.72 mg/kg over 7 days (intestinal larval and adult stages) or 0.36 mg/kg over 14 days (intestinal larval and adult stages)

## 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.

# 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)