Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Gallifen 40 mg/g Premix for Medicated Feeding Stuff for Chickens and Pheasants

Date Created: 29/03/2017
Updated for additional species (pheasants) November 2018
Updated for additional User Safety precautions December 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0608/001/DC
Name, strength and pharmaceutical form	Gallifen 40 mg/g Premix for Medicated Feeding Stuff for Chickens
Applicant	Huvepharma N.V. Uitbreidingstraat 80 Antwerpen B-2600 Belgium
Active substance(s)	Fenbendazole
ATC Vetcode	QP52AC13
Target species	Chickens – Can be used in chickens in lay. Pheasants - The safety of the product has not been evaluated in breeding pheasants. Therefore in these birds use only according to the benefit/risk assessment by the responsible veterinarian.
Indication for use	Treatment of chickens infected with *Heterakis gallinarum* (L5 and adult stages) and *Ascaridia galli* (adult stage). Treatment of pheasants infected with *Heterakis gallinarum* (adult stages).

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 'hybrid' application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	23/11/2016
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	BE, BG, FR, HU, IE, IT, NL, PL, PT, RO, ES

I. SCIENTIFIC OVERVIEW

This was an application for a generic 'hybrid' product, in accordance with Article 13(3) of Directive 2001/82/EC, as amended. This was determined a generic 'hybrid' application because changes to the pharmaceutical form with regard to the reference medicinal product have been made and therefore bioequivalence to the reference product could not be demonstrated. The reference product is Panacur AquaSol 200 mg/ml Oral Suspension for use in drinking water for Pigs and Chickens, authorised in the UK since 2011.

The product is indicated for use in chickens, for the treatment of infections of *Heterakis gallinarum* (L5 and adult stages) and *Ascaridia galli* (adult stage), and in pheasants[1], for the treatment of *Heterakis gallinarum*, (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.[2] 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 [3] 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] Pheasant, a minor species, were added to the authorisation via a variation procedure in November 2018.
[2] SPC – Summary of product Characteristics.
[3] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains fenbendazole *(40 mg)* and the excipients maize starch and pregelatinised starch.

The container/closure system consists of a polyethylene-aluminium-paper/paper/paper bag containing 20 kg and polyethylene/aluminium foil/polyethylene terephthalate zipper bags containing, 1, 2 or 5 kg. 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 homogenization of the active substance and maize starch followed by granulation, sieving and grinding before being filled into containers. 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 is supplied in accordance with a current Ph.Eur. Certificate of Suitability.

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 and the polyethylene bags inside a fibre or polyethylene drum 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 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. 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, colour, related substances, particle size and microbiological quality.

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. A re-test period of 2 years in approved via the Ph. Eur. Certificate of Suitability. Available stability data on the finished product supports a shelf life of the product as packaged for sale of 3 years.

The claim of a 3 month shelf life after first opening the immediate packaging is based on the demonstration of stability for three batches stored in both approved package types stored at 20-25°C for 18 and 30 months.

The claim of a 3 month shelf life after incorporation into meal or pelleted feed is acceptable based on stability data and advice in Section 4.9 of the SPC regarding recommendation to premix the product at a ratio of 1:10 with feed ingredients before blending into the final feed.

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: 1 month.

Veterinary medicine product as packaged for sale: no special storage precautions.

After first opening of the immediate packaging: do not store above 25°C.

Medicated feed (mashed): no special storage precautions.

Medicated feed (pelleted): do not store above 25°C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the nature of the application, pharmacological and toxicological data are not required.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. 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.
- Accidental ingestion of the product should be avoided.
- In the event of accidental ingestion, rinse mouth with plenty of clean water and seek medical advice.
- This product may cause eye irritation and skin sensitisation.
- Avoid contact with the eyes and skin.
- 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

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

Phase I:

The initial predicted environmental concentration (PEC) in soil is less than 100 µg/kg. A phase II ERA was therefore not required. The product is not expected to pose a risk for the environment when used in accordance with the recommendations included in the SPC.

III.B.2 Residues documentation

Residue Studies

Residue depletion studies using the final formulation have been conducted in chickens. Samples of tissues 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 meat and offal withdrawal period. The analytical method was UHPLC-MS/MS[4]. The method was fully validated.

The product is not authorised for use in laying birds producing eggs for human consumption.

MRLs

MRLs for fenbendazole have been established for edible tissues/milk/eggs. The marker substance is oxfendazole sulphone.

MRLs are listed below:

	All food producing species except fish.
Muscle	50 µg/kg
Fat	50 µg/kg
Liver	500 µg/kg
Kidney	50 µg/kg
Milk	10 µg/kg
Eggs	1300 µg/kg

Withdrawal Periods

A withdrawal period of 8 days meat in chickens is justified. Do not use in pheasants for hunting for at least 8 days after medication.

Eggs: zero days.

IV CLINICAL DOCUMENTATION

This was 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 (chicken), 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 determination and dose confirmation studies in which the efficacy of Gallifen 40 mg/g Premix for Medicated Feeding Stuff against *Heterakis gallinarum* and *Ascarida galli* was determined.

[4] Ultra high-performance liquid chromatography-tandem mass spectrometry.

IV.I. Pre-Clinical Studies

Pharmacology

Bibliographical data has been provided which show that fenbendazole is an anthelmintic belonging to the benzimidazole class. It acts by binding to beta-tubulin, from which microtubles are formed. Microtuble loss at the intestinal level in nematodes results in loss of transport of secretory vesicles and decreased glucose uptake, followed by cellular disintegration.

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. The metabolic pathway of Fenbendazole and its metabolites is via oxidation in the liver. Elimination of Fenbendazole is primarily via the faeces and to a small extent in the urine. Fenbendazole is metabolised to its sulphoxide (oxfendazole) and further to oxfendazole sulfone.

Tolerance in the Target Species

The applicant has conducted a target animal tolerance study in chickens using multiples of the recommended dose in the target species. No treatment was used as a control. The investigation product, which was identical in formulation to the authorised product, was incorporated into a complete broiler feed prior to the start of the study. Parameters evaluated were mortality, bodyweight, feed and water consumption, clinical observation, physical examination and blood samples. No adverse effects were seen following doses of up to five times the recommended dose over five consecutive days.

Resistance

Based on the information provided there appears to be little evidence of benzimidazole resistance in chicken nematodes. However, as the development of resistance cannot be ruled out, adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory/Field Trials

In chickens, the applicant conducted two dose determination studies and two dose confirmation studies to support a dose of 1 mg fenbendazole per kg bodyweight per day for 5 consecutive days.

During a variation approved in November 2018, pheasants were added as a target species. As pheasants are considered a minor species, redacted data were permitted. The following studies were performed:

- A pilot study to determine an artificial infection model with *H. gallinarum* in pheasants treated with fenbendazole-medicated feed. RESULT: Successful artificial infection model for *H. gallinarum* in pheasants, using infective stages from two different sources (chickens and pheasants). In addition, supportive evidence of efficacy (>90%) of the proposed dosing regimen was demonstrated.

- A dose determination study to assess the efficacy of three different dose levels (0.5, 1.0 and 1.5 mg fenbendazole per kg bodyweight per day once daily for five consecutive days) against artificial infections with *H. gallinarum* in pheasants. RESULT: Supportive evidence of efficacy of three different fenbendazole dosing regimens: 0.5, 1.0 and 1.5 mg fenbendazole per kg bodyweight once daily for five consecutive days, against adult *H. gallinarum* infections in pheasants.

- A dose confirmation study to confirm the efficacy of a dose of 1.0 mg fenbendazole per kg bodyweight per day once daily for five consecutive days against artificial infections with *H. gallinarum* in pheasants. RESULT: A daily dose of 1 mg fenbendazole per kg b.w. per day administered in feed for 5 consecutive days was supported.

- A ‘field study’ to confirm the efficacy of a dose of 1.0 mg fenbendazole per kg bodyweight per day once daily for five consecutive days against artificial infections with *H. gallinarum* in pheasants. RESULT: A daily dose of 1 mg fenbendazole per kg b.w. per day administered in feed for 5 consecutive days provided sufficient clinical efficacy in pheasants.

Dose confirmation studies:

Study title	Dose confirmation study for fenbendazole 40 mg/g premix for medicated feed against an artificial infection with *Ascaridia galli* in layer chickens.
Objectives	To confirm the efficacy of fenbendazole 40 mg/g premix for medicated feed when given at a dose level of 1.0 mg fenbendazole per kg bodyweight per bird per day over five consecutive days against an artificial infections with the nematode parasite *A. galli* in layer chickens.
Test site(s)	Single site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 40 mg/g premix for medicated feed. Administered with feed on five consecutive days at a dose of 1.0 mg/kg bodyweight per day.
Control product/placebo	No treatment.
Animals	30 day old female chicks Inclusion Criteria Clinically healthy Exclusion Criteria Unhealthy animals
Outcomes/endpoints	Reduction in worm count
Randomisation	Randomised.
Blinding	Blinded.
Method	Acclimatisation period (minimum 2 weeks) Animals experimentally infected with *A. galli* eggs. Bodyweight was monitored and treatment with Fenbendazole 40 mg/g premix was given daily. Post treatment clinical observations were recorded daily.
Statistical method	An analysis of variance was used to assess differences between the treatment groups. Difference between groups were considered significant when $p \leq 0.05$.
RESULTS	
Outcomes for endpoints	Worm count – efficacy was 95% for the treatment group. There was a significant difference ($p<0.001$) between the number of worms recovered from the treatment groups. No significant adverse events were reported.
DISCUSSION	Fenbendazole 40 mg/g premix administered at 1.0 mg/kg for five days was efficacious in reducing the number of *A. galli* adult worms in experimentally infected birds.

Study title	Dose confirmation study for fenbendazole 40 mg/g premix for medicated feed against artificial infections with *Heterakis gallinarum* in layer chickens.
Objectives	To confirm the efficacy of fenbendazole 40 mg/g premix for medicated feed when given at a dose level of 1.0 mg fenbendazole per kg bodyweight per bird per day over five consecutive days against an artificial infections with the nematode parasite *H. gallinarum* in layer chickens.
Test site(s)	Single site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 40 mg/g premix for medicated feed. Administered with feed on five consecutive days at a dose of 1.0 mg/kg bodyweight per day.
Control product/placebo	No treatment.
Animals	30 day old female chicks Inclusion Criteria Clinically healthy Exclusion Criteria Unhealthy animals
Outcomes/endpoints	Reduction in worm count
Randomisation	Randomised.
Blinding	Blinded.
Method	Acclimatisation period (minimum 2 weeks) Animals experimentally infected with *H. gallinarum* eggs. Bodyweight was monitored and treatment with Fenbendazole 40 mg/g premix was given daily. Post treatment clinical observations were recorded daily.
Statistical method	An analysis of variance was used to assess differences between the treatment groups. Difference between groups were considered significant when $p \leq 0.05$.
RESULTS	
Outcomes for endpoints	Worm count – efficacy was 96.2% for the treatment group. There was a significant difference ($p<0.001$) between the number of worms recovered from the treatment groups. No significant adverse events were reported.
DISCUSSION	Fenbendazole 40 mg/g premix administered at 1.0 mg/kg per day for five days was efficacious in reducing the number of *H. gallinarum* adult worms in experimentally infected birds.

Hybrid dose confirmation/semi-field study

Study title	A field study to confirm the efficacy of fenbendazole 40 mg/g premix for medicated feed against natural infections of *Ascaridia galli* and *Heterakis gallinarum* in layer chickens.
Objectives	The objective of this study was to confirm the efficacy of fenbendazole 40 mg/g premix for medicated feed in a field study when administered at a dose level of approximately 1.0 mg fenbendazole per kg bodyweight on a flock basis over five consecutive days against natural infections with the nematode parasites *A. galli* and *H. gallinarum* in layer chickens. The study aimed to reflect field scale commercial conditions for layer chickens and included an untreated control flock. Efficacy was evaluated by necropsy and worm counts at study completion.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 40 mg/g premix for medicated feed. Administered with feed on five consecutive days at a dose of 1.0 mg/kg bodyweight per day.
Control product/placebo	No treatment
Animals	1115 *Gallus gallus domesticus* in-lay chickens, approximately 18 months old from a single flock. Known to have co-infections of *A. galli* and *H gallinarum*. No prior history of anthelmintic treatment. Inclusion Criteria Clinically healthy Exclusion Criteria Unhealthy birds
Outcomes/endpoints	Reduction in worm count.
Randomisation	Randomised
Blinding	Personnel performing faecal egg and parasite counts were blinded.
Method	Birds were divided into two groups – treated and non-treated. The treated group received a measured quantity of medicated feed daily for five days. Bodyweight of randomly selected birds was monitored at Study day -7, 0, 7 and 10. Random faecal sampling was carried out for both groups at days 0, 5 and 10. At the end of the study, worms were counted from the caecal and small intestine contents.

Statistical method	An analysis of variance was used to assess differences between the treatment groups. Difference between groups were considered significant when $p \leq 0.05$.
RESULTS	
Participant flow	Bodyweights for birds in both groups remained similar throughout the study. Satisfactory efficacy (>90%) was obtained against the adult stages of both target parasites with a statistically significant difference between treatment and control groups ($p<0.05$). Satisfactory efficacy of immature L5 *H. gallinarum* worm counts (95% confidence limit) was obtained. No significant adverse events were reported.
DISCUSSION	Fenbendazole 40 mg/g premix administered at 1.0 mg/kg per day for five days was efficacious in reducing the number of adult *A. galli* and *H. gallinarum* adult worms and immature L5 stages of *H. gallinarum* in experimentally infected birds.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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