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Publicly Available Assessment Report for a
Veterinary Medicinal Product

Gallifen 200 mg/ml suspension for use in drinking water for chickens and pheasants

PRODUCT SUMMARY

EU Procedure number	IE/V/0579/001 (formerly UK/V/0644/001)
Name, strength and pharmaceutical form	Gallifen 200 mg/ml suspension for use in drinking water for chickens and pheasants
Active substances(s)	Fenbendazole
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Legal basis of application	Hybrid application (Article 13(3) of Directive 2001/82/EC)
Date of Authorisation	31 January 2018 (UK) 29 March 2018 (IE)
Target species	Chickens, pheasants
Indications for use	Treatment of chickens infected with *Heterakis gallinarum* (adult stages), *Ascaridia galli* (adult stages), *Capillaria obsignata* (adult stages) or *Raillietina echinobothrida* (adult stages). Treatment of pheasants infected with *Heterakis gallinarum* (adult 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, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, UK(NI).

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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 chickens 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 chickens infected with *Heterakis gallinarum* (adult stages), *Ascaridia galli* (adult stages), *Capillaria obsignata* (adult stages) or *Raillietina echinobothrida* (adult stages). The product is also indicated for the treatment of pheasants infected with *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. 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 as 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 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.

Toxicological 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 chickens 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.
Concerning the use of the VMP for the treatment of chickens infected with *Raillietina echinobothrida* at a dose of 3 mg fenbendazole / kg bodyweight per day for 10 consecutive days, the PEC_{soil} value for broilers exceeded the threshold of 100 µg/kg, although it is noted that intensively reared broiler chickens are unlikely to be infected with *R. echinobothrida*. Relevant

information concerning restrictions on use of the VMP at this dose in broiler chickens is included in sections 3.4 and 3.5 of the SPC.

III.B.2 Residues documentation

Residue Studies

The applicant conducted appropriate residue depletion studies. Four GLP-compliant residue depletion studies in chickens, for tissues and eggs, were submitted. All studies were in accordance with current VICH. The test birds were administered the test product daily in medicated drinking water and received the recommended dose for the recommended duration. Suitable analysis was performed.

A zero day withdrawal period in eggs was proposed on the basis that all residues were below the LOQ (1/2 MRL) at every time point, both during and after treatment.

Concerning the use of the VMP for the treatment of chickens infected with *Raillietina echinobothrida* at a dose of 3 mg fenbendazole / kg bodyweight per day for 10 consecutive days, 2 GLP-compliant residue depletion studies in chickens (investigating residue depletion in tissues and eggs) were provided. Both studies were in accordance with current VICH guidance. The test birds were administered the VMP daily in medicated drinking water and received the recommended dose for the recommended duration. Suitable analysis was performed and withdrawal periods for the dose rate of 3 mg / kg bw / day for 10 days were determined based on the results of these studies.

MRLs

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

Marker residue: Sum of extractable residues which may be oxidised	All food-producing species except fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'
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

Chickens:
Meat and offal:
6 days for the dosage 1 and 2 mg fenbendazole / kg bodyweight / day.
8 days for the dosage 3 mg fenbendazole / kg bodyweight / day.
Eggs: zero days

Pheasants:
Meat and offal: 6 days
Do not release pheasants for hunting for at least 6 days after the end of medication.
Eggs: zero days

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

The applicant conducted studies to evaluate the safety of the product in chickens. No adverse effects were noted at 1x, 3x and 5x the recommended dose.
Concerning the use of the VMP for the treatment of chickens infected with *Raillietina echinobothrida* at a dose of 3 mg fenbendazole / kg bodyweight per day for 10 consecutive days, 3 target animal safety studies investigating 1X, 4X and 6.6X the

recommended dose were performed. The SPC accurately reflects all adverse effects that were observed (following overdose only) from these studies.

Resistance
Adequate warnings and precautions appear in the product literature.

IV.II. Clinical Documentation
Laboratory Trials
The applicant submitted pilot and pivotal dose confirmation studies to confirm the efficacy of 1.0 mg fenbendazole/kg/bodyweight/day once daily for 5 consecutive days against artificial infections of *A. galli* and subsequently of *H. gallinarum* in layer chickens. A field study, (together with suitable published literature), was also submitted, which assessed the efficacy of the product at 0.1 mg fenbendazole/kg/bodyweight/day once daily for 5 consecutive days.
In addition, the applicant submitted two pivotal dose confirmation studies which confirmed the efficacy of 2.0 mg fenbendazole/kg bodyweight/day once daily for 5 days against natural infections of *C. obsignata* in layer chickens.

Pivotal dose confirmation studies:

(1) Study title	Dose confirmation study for fenbendazole 200 mg/ml oral suspension against an artificial infection with *A. galli* in layer chickens
Objectives	To determine the efficacy of fenbendazole 200 mg/ml oral suspension when given at a dose level of 1.0 mg fenbendazole per kg bodyweight per day for five consecutive days against artificial infections with the nematode parasite *A. galli* in layer chickens.
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	43 domestic one day old (Day 0) healthy chicks
Randomisation	Randomisation was performed based on 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	Birds were group-housed prior to a 2-week acclimatisation. All were clinically assessed on day 0. The proposed product was administered at a dose rate of 1.0 mg/kg/bodyweight/day for 5 consecutive days via drinking water. 1. Untreated control group 2. Proposed product administered as described above Birds were challenged with 200 *A. galli* eggs per bird, administered at Day 0. On Days 39 to 43, birds in group 2 received the medication. Birds in group 1 continued to receive unmedicated water.
Statistical method	The statistical unit was the cage, as birds were housed in groups of four during treatment. Adult *A. galli* worm counts were log transformed prior to statistical analysis using $\log_{10}(\text{Count}+1)$ in order to allow for zero counts. An analysis of variance was used to assess differences between the treatment groups. The means from the log transformed data with confidence intervals were back-transformed to give geometric means. The percentage reduction in worm counts was calculated for the treated

	groups 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 adequacy of the parasite infection observed in the untreated control birds was assessed and 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. The primary efficacy criterion was the adult *A. galli* worm counts at necropsy. The results of the statistical analysis were interpreted at the 5% ($p<0.05$) level of statistical significance.
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	Dose confirmation study for fenbendazole 200 mg/ml oral suspension against an artificial infection with *H. gallinarum* in layer chickens
Objectives	To determine the efficacy of fenbendazole 200 mg/ml oral suspension when given at a dose level of 1.0 mg fenbendazole per kg bodyweight per day for five consecutive days against artificial infections with the nematode parasite *H. gallinarum* in layer chickens.
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	39 domestic one day old healthy chicks (Day 17)
Randomisation	Randomisation was performed based on 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	Birds were group-housed prior to a 17 day acclimatisation. All were clinically assessed on day 0. The proposed product was administered at a dose rate of 1.0 mg/kg/bodyweight/day for 5 consecutive days via drinking water. 1. Untreated control group 2. Proposed product administered as described above Birds were challenged with 200 *H. gallinarum* eggs per bird, administered at Day 0. On Day 30, birds in group 2 received the medication. Birds in group 1 continued to receive unmedicated water.
Statistical method	The statistical unit was the cage as birds were randomly allocated to numbered cages (maximum of four birds per cage) during the treatment period.

	Adult *H. gallinarum* worm counts were log transformed prior to statistical analysis using $\log_{10}$(Count+1) to compare the two treatment groups using a hierarchical model to allow for cage effects. Results were back-transformed to give geometric means and 95% confidence limits on the original scale. The percentage reduction in worm counts was calculated for the treated group 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 adequacy of the parasite infection observed in the untreated control birds was assessed and 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. The primary efficacy criterion was the adult *H. gallinarum* worm counts at necropsy. The results of the statistical analysis were interpreted at the 5% ($p<0.05$) level of statistical significance.
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.

Field Trials

Study title	A field study to confirm the efficacy of fenbendazole 200 mg/ml Oral Suspension against natural infections of *A. galli* and *H. gallinarum* in layer chickens
Objectives	The objective of this study was to confirm the efficacy of fenbendazole 200 mg/ml oral suspension when given 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.
Test site(s)	United Kingdom
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fenbendazole 200 mg/ml oral suspension
Control product/placebo	Untreated animals
Animals	1217 healthy end of lay chickens approximately 18 months old. Naturally infected birds.
Randomisation	Birds randomly divided into two groups.
Blinding	Due to the appearance of the proposed product, blinding was performed only for personnel assessing parasite numbers.
Method	Day 0-4 birds in the group to receive product were given the target daily dose of 1.0 mg/kg/bodyweight for 5 consecutive days. Control birds received unmedicated water only. Sampling of birds occurred at stipulated time points.
Statistical method	Adult *A. galli* and *H. gallinarum* worm counts were log transformed prior to statistical analysis using $\log_{10}$(Count+1) in order to allow for zero counts. An analysis of variance was used to assess differences between the two flocks (T01 and

	T02). The means (and confidence intervals) from the log transformed data were back-transformed to give geometric means. The percentage reduction in *A. galli* and *H. gallinarum* worm counts were calculated for the treated flock (T02) 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 primary efficacy criteria were the adult *A. galli* and *H. gallinarum* worm counts at necropsy. Other measurements, such as immature worm counts, mortality etc. were summarised statistically as appropriate. The results of the statistical analysis were interpreted at the 5% ($p<0.05$) level of statistical significance.
RESULTS	In all cases, statistically significant differences equating to $p<0.05$ was obtained. Mean efficacy was > 90%.
Adverse events	One adverse event was considered to be 'unclassifiable' five other events were considered to be unrelated to treatment.
DISCUSSION	Satisfactory efficacy was obtained between treatment and control groups, with a statistically relevant difference in counts of appropriately mature larvae for both target species.

Concerning the use of the VMP for the treatment of chickens infected with *Raillietina echinobothrida,* 2 pilot and 2 pivotal dose confirmation studies were submitted.
The two pivotal GCP-compliant dose confirmation studies were conducted in laying hens with naturally acquired infections in Belgium, and investigated efficacy of the proposed dose of 3 mg / kg per day for 10 consecutive days for the treatment of *Raillietina echinobothrida* and *Raillietina* spp. In the study evaluating efficacy against *R. echinobothrida* only, a higher dose of 5 mg / kg per day for 10 consecutive days was also investigated.
Based on the results of the pivotal dose confirmation studies, it is accepted that efficacy of the VMP Gallifen 200 mg/ml oral suspension at the proposed dose of 3 mg / kg per day for 10 consecutive days for the treatment of *Raillietina echinobothrida* (adult stages) has been demonstrated (based on reported percent efficacy values of >90%). Whilst clinical field data were not submitted, the isolates of Raillietina echinobothrida for which efficacy was demonstrated were considered representative of the target pathogen across the EU and this was considered suitable justification for the omission of clinical field trial data.

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.

VI. 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 HPRA website.
This section 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.

Summary of change (Application number)	**Approval date**
Addition of pheasants as a target species (UK/V/0644/001/DX/001)	30/04/2019
Addition of a new indication: treatment of chickens infected with *Capillaria obsignata* (adult stages) (IE/V/0579/001/II/002)	14/10/2021
Addition of a new indication: treatment of chickens infected with *Raillietina echinobothrida* (adult stages) (IE/V/0579/001/A/005/G)	09/08/2023