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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Panacur AquaSol (EMA/V/C/002008/X/0003)

International non-proprietary name: fenbendazole

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.



Introduction

An application for an extension to the Community marketing authorisation for Panacur AquaSol was submitted by Intervet International B.V. to the European Medicines Agency (the Agency) on 13 December 2012 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 3 thereof. The rapporteur appointed was G. J. Schefferlie and co-rapporteur H. K. Ostensen.

The already authorised product, Panacur AquaSol, indicated for the treatment and control of gastro-intestinal nematodes in pigs, was authorised for use in the Community on 9 December 2011.

Panacur AquaSol contains fenbendazole as the active substance and is presented in packs/containers of 1 bottle in two different sizes 1 litre and 4 litres. The route of administration for this oral suspension is for use in drinking water. This extension application concerns addition of a food-producing target animal species to extend the use of Panacur AquaSol to include chickens with the following indication: *Chicken*:

Treatment of gastro-intestinal nematodes in chicken infected with:

- *Ascaridia galli (L5 and adult stages)*
- *Heterakis gallinarum (L5 and adult stages).*

The CVMP adopted an opinion and CVMP assessment report on 15 January 2014.

On 14 March 2014, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Panacur AquaSol is manufactured, packaged and released by Intervet Productions Igoville.

The Agency Compliance and Inspection Sector has reviewed the manufacturer information contained in the application form (Part 1A) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorisations or valid GMP (good manufacturing practice) certificates as appropriate. Hence, no GMP inspections are deemed necessary at this stage within the scope of this extension application.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are in line with legal requirements.

Part 2 - Quality

Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken is identical to Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for pigs in all aspects of the formulation, manufacture, control testing, type of packaging and pack sizes. Hence a full Part 2 for the dossier is not submitted and reference is made to the quality data submitted and approved previously.

Part 3 – Safety

The safety of fenbendazole has been studied and described in detail. Laboratory animal data generated with the active substance were assessed as part of the MRL (maximum residue limit) evaluations and are presented in the published CVMP MRL reports on fenbendazole (e.g., EMA/MRL/193/97-FINAL). Consequently these studies are not described in detail here.

Fenbendazole has been licensed world-wide for the treatment and control of helminth infections in food and non-food producing animal species for more than 30 years and its safety is well established.

In vivo, fenbendazole mainly exists in its oxidized oxfendazole form. The ADI (acceptable daily intake) for fenbendazole has been adopted from oxfendazole. This ADI of 7 µg/kg of bodyweight (bw) per day was established by applying a safety factor of 100 to the no-observed-effect level (NOEL) of 0.65 mg/kg bw per day for hepatic vacuolation seen in a carcinogenicity study in rats treated with oxfendazole.

Safety documentation

Pharmacodynamics

Benzimidazoles inhibit the polymerisation of tubulin to microtubules, interfering with essential structural and functional properties of nematode cells, such as cytoskeleton formation and transport of nutrients. The uptake of glucose is reduced and interference with mitochondrial reactions leads to a reduction of availability of adenosine triphosphate (ATP).

Benzimidazoles have an ovicidal effect on *Trichonstrongylus* type eggs as well as on *Ascaris suum* eggs. This effect is thought to be caused by the inhibition of microtubule formation, already at a very early stage of egg development, which would be *in utero* for *Ascaris*.

Fenbendazole was introduced in 1974 as Panacur and has shown to be effective against nematode infections in many animal species.

See also Part 4.

Pharmacokinetics

The information provided by the applicant is similar to the information as provided during the procedure for the initial marketing authorisation (EMA/V/C/002008). Additional data on the target species chicken as recently assessed by the CVMP for the purpose of extending the fenbendazole tissue MRLs to chickens were provided. The study is reported in the European Public MRL Assessment Report on fenbendazole (EMA/CVMP/914694/2011).

Due to its poor solubility, there is limited absorption of fenbendazole from the intestine after oral administration. The extent of absorption differs among species, i.e. 27% for pigs, 20% for cattle, 24% for goats, 10% for turkeys, 16% for chickens, 18% for rabbits (Petersen and Friis, 2000; Davis et al., 1988).

The oral bioavailability is increased to a limited extent (1.3 times) when fenbendazole is formulated as Panacur AquaSol. The wet-milling process appeared not to affect metabolism, disposition or elimination of fenbendazole.

Fenbendazole and its metabolites are distributed throughout the body and highest concentrations are found in the liver (Heggem, 2008).

After absorption, fenbendazole is rapidly metabolised by liver microsomes. The first metabolite is oxfendazole, which results from sulfoxidation. This metabolism step is reversible. Oxfendazole is further sulfoxidated to oxfendazole sulfone. Fenbendazole can also be demethoxycarbonylated to fenbendazole amine or hydroxylated to p-hydroxyfenbendazole (Short *et al.*, 1988).

Moreover, a metabolism study conducted with radiolabeled fenbendazole showed that the metabolic pathway of fenbendazole in chickens is the same as in mammals. The residues fenbendazole, oxfendazole and oxfendazole sulfone were found in eggs.

See also Part 4.

Toxicological studies

Single dose toxicity

Oral single dose studies in mice, rats, rabbits and dogs demonstrate that fenbendazole is of low acute toxicity. The study results did not allow the derivation of no-observed-adverse-effect levels (NOAELs).

Repeat dose toxicity

Data on repeat dose toxicity are available from rats and dogs. The overall NOAEL was 4 mg/kg bw/day, based on lymphoid hyperplasia observed in dogs.

Tolerance in the target species of animal

Please refer to Part 4. No points of concern relevant for the safety of fenbendazole in humans could be identified.

Reproductive toxicity/Developmental toxicity

The MRL summary reports describe a 3-generation study in rats, from which a NOAEL of 15 mg/kg bw/day was derived, based on diarrhoea, reduced bodyweight gain and pathological changes in the liver, as well as reductions in fertility, survival and growth of the neonates during lactation.

Fenbendazole had no effect in testicular function tests in sheep and horses.

The teratogenicity studies in rats and rabbits described in the MRL summary report (EMA/MRL/193/97-FINAL) showed no evidence of foetotoxicity or teratogenicity in rats at any dose level, but for rabbits, a NOAEL of 25 mg/kg was established, based on an increase in delayed ossification in the 63 mg/kg bw group.

There were no treatment-related effects in the offspring of dogs, pigs, sheep and cattle, administered fenbendazole at various times during gestation.

Mutagenicity/genotoxicity

Based on a battery of *in vitro* and *in vivo* genotoxicity tests, described in the MRL summary report, it was concluded that fenbendazole is not genotoxic.

Carcinogenicity

No data on carcinogenicity are deemed necessary, because fenbendazole is devoid of genotoxic potential, has no structural alerts for carcinogenicity, and no evidence for carcinogenicity was found in a 2-year study in mice.

Studies of other effects

Studies with fenbendazole showed that the substance can be considered practically non-irritating to the skin and eyes. Fenbendazole was not a skin sensitiser when tested in a 10% formulation in guinea pigs.

Fenbendazole seems to be well tolerated in humans after oral exposure (single oral dose up to 2,000 mg/per person; 500 mg/per person for 10 consecutive days); however observations in humans are limited.

User safety

Hazard characterization

Fenbendazole is of low acute toxicity after oral exposure. No acute exposure limit is available.

Based on limited human data it appears that doses up to 500 mg per person did not result in adverse effects. Moreover, single doses up to 2,000 mg per person were reported to cause no adverse effects.

Fenbendazole is not expected to have a skin or eye irritating potential at concentrations up to 10%, although, in the final formulation fenbendazole is present at a concentration of 20%. It is considered unlikely that the final formulation will have skin or eye irritating/damaging effects.

Warning sentences are included in the summary of product characteristics (SPC) as if the final formulation had a skin sensitising property. This was considered sufficient to compensate for the fact that the skin sensitisation test was performed with a lower concentration of fenbendazole than in the final solution.

The excipients are considered to be of low toxicity after systemic exposure.

Exposure

This product will be used by professional users (veterinarians and farmers).

Tasks and situations that may lead to an exposure are removal of the seal from the opening of the bottle, decanting the suspension into a measuring device, transfer of the pre-diluted suspension from the measuring device into the pre-dilution tank or into the medication tank, stirring the (diluted) suspension, control of the drinkers for flow of medicated water and cleaning of the measuring device.

Dermal (direct skin contact) and eye exposure (splashes) are considered the relevant routes of exposure to Panacur AquaSol. The total amount of fenbendazole which might come into contact with the user's skin per administration is calculated to be 1,561 mg per person (i.e. 26 mg/kg bw). As no dermal bioavailability data are available for the suspension, a worst case bioavailability of 100% was used by the CVMP and subsequently resulted in an internal exposure of 26 mg/kg bw. Oral exposure (due to hand-to-mouth contact) and eye exposure (due to hand-to-eye contact) are considered

negligible as this product will be used by professionals. The risk of accidental exposure by children is mitigated by a child resistant closure.

Risk characterisation

Skin/eye irritation:

Fenbendazole is not considered to have skin or eye irritating potential at concentrations up to 10%. In the final formulation fenbendazole is present at a concentration of 20%. However, because of the absence of effects at 10%, it is considered unlikely that the final formulation will have skin or eye irritating/damaging effects. Further, safety measures are already proposed which would normally be acceptable for a formulation with skin and eye irritating properties. Because of the low concentrations in the final formulation, also no skin and/or eye irritating effects are expected to occur from the excipients.

Sensitisation:

Fenbendazole did not cause hypersensitivity reactions in a sensitisation test, however this study was not performed with the final formulation. Due to the higher concentration in the final formulation compared to the tested formulation and the difference in excipients it is questioned whether the test result is relevant for the final formulation. However, safety measures are already proposed which would normally be acceptable for formulations with sensitising properties, and a warning sentence with respect to hypersensitivity reactions and the recommendation of wearing of gloves are included in the SPC section 4.5. Also, for the excipients hypersensitivity reactions cannot be excluded.

Systemic adverse effects (after dermal exposure):

The estimated exposure (26 mg/kg bw) was compared to several NOAELs (e.g. 2,500 mg/kg bw derived from the 30-day rat study, 125 mg/kg bw derived from the 90-day dog study). No data were available on absorption via the skin and to estimate the internal NOAEL, an oral bioavailability of 27% (F_{oral} pigs) was assumed, resulting in internal NOAELs of respectively 675 and 34 mg/kg bw.

The estimated exposure was also compared to human tolerable doses, i.e. 8.3 mg/kg (corresponding to an internal dose of 2.3 mg/kg bw.) for 10 consecutive days, and single doses up to 33 mg/kg bw (corresponding to an internal dose of 9 mg/kg).

The calculated margin of exposure (MOE) is below the margin that is generally used to account for inter- and/or intraspecies variation. The wearing of gloves will decrease the exposure with a factor 10 (i.e. 2.6 mg/kg bw) and subsequently increase the calculated MOEs by a factor 10. Then, still some MOEs would be below 100 or 10. Worst case MOEs (with gloves) of 3 and 2 could be calculated (when considering the human data).

However, it is acknowledged that the NOAELs were obtained from studies administering fenbendazole over a longer period, while Panacur AquaSol will be administered during 5 consecutive days. The NOAEL in some studies was established on the highest dose tested. Also, the data on single dose toxicity of fenbendazole show that fenbendazole is of low toxicity. Finally, a dermal bioavailability of 100% was used for the estimation of dermal exposure is very worst case.

Considering all available information, the CVMP believes that the product can be safely used by professionals if protective gloves are worn. Moreover, the warning and safety measures include a statement in the SPC that contaminated clothes should be removed after spillage.

The occurrence of effects on human fetuses cannot be fully excluded. Even when wearing gloves, decreasing the exposure by a factor 10, the MOE is far below 100 (i.e. MOE of 3). Refining the worst case dermal bioavailability (e.g. 27% instead of 100%) does still result in a MOE < 100. During

procedure EMEA/V/C/002008 (authorisation for pigs) it was concluded that the delayed ossification (reflecting growth retardation) would most likely require daily exposures for a longer period of time (the product posology included only a 2-day treatment). However, the duration of treatment is now (for chicken) 5 days. It should be noticed that the adverse effects (palatoschisis, hypoplastic kidneys, abnormal caudal vertebrae, aplastic thumbs, fragmented sacral vertebrae, knotty swellings in clavicles) were observed in foetuses of the rabbit, while the general state of health was normal for dams, which could point to a direct effect on the foetus. These effects occurred at 63 mg/kg bw; no higher doses (resulting in more severe or additional effects) were tested. It is further noted that oxfendazole (predominant metabolite of fenbendazole) caused early resorptions and malformations in a range-finding developmental toxicity study in the rabbit at 100 mg/kg bw/day (JECFA 41, <http://www.inchem.org/documents/jecfa/jecmono/v041je03.htm>). It cannot be excluded that these effects are the result of a single exposure to fenbendazole.

Therefore, a warning sentence with respect to handling of the product by pregnant women has been included in the SPC - 'Pregnant women must take extra precautions when handling this veterinary medicinal product'.

Environmental risk assessment

Phase I

A Phase I environmental risk assessment (ERA) for Panacur AquaSol was performed in accordance with VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline GL6 (CVMP/VICH/592/98-FINAL) and CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

This ERA was limited to the addition of the new target species chicken, for the treatment and control of pre-adult and adult stages of *Ascaridia galli* and *Heterakis gallinarum*, because the addition of a new food producing species may result in an increase in exposure of the environment.

The dosage for chickens is 1.0 mg fenbendazole/kg bw, administered on five consecutive days.

For Panacur AquaSol, none of the questions 1–6 and 14 of the decision tree allow for a stop in Phase I. Consequently the initial predicted environmental concentration in soil (PEC_{soil}) was calculated in line with CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), based on a dose of 1.0 mg fenbendazole/kg bw administered on 5 consecutive days.

Initial PEC_{soil} were calculated to be 2.79 $\mu\text{g}/\text{kg}$ for broiler breeder, 5.18 $\mu\text{g}/\text{kg}$ for laying hen, 9.82 $\mu\text{g}/\text{kg}$ for replacement layer and 44.35 $\mu\text{g}/\text{kg}$ for broiler. All initial PEC_{soil} are below the trigger of 100 $\mu\text{g}/\text{kg}$, and therefore the ERA can stop in Phase I, no further assessment is needed.

In conclusion, based on the data provided the ERA can stop at Phase I. Panacur AquaSol is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Fenbendazole is of low acute toxicity after oral exposure. No acute exposure limit is available.

In vivo, fenbendazole mainly exists in its oxidized oxfendazole form. The ADI for fenbendazole has been adopted from oxfendazole. This ADI of 7 $\mu\text{g}/\text{kg}$ bw/day was established by applying a safety

factor of 100 to the NOAEL of 0.65 mg/kg bw/day for hepatic vacuolation seen in a carcinogenicity study in rats treated with oxfendazole.

The NOAEL for developmental effects was set to 15 mg/kg bw/day, based on an increase in delayed ossification in the 63 mg/kg bw group. There was no evidence of foetotoxicity or teratogenicity in rats, dosed at levels of 25, 250 or 2,500 mg/kg bw/day. For rabbits, a NOAEL of 25 mg/kg was established.

Fenbendazole is not considered to be genotoxic and/or carcinogenic.

Fenbendazole seems to be well tolerated in humans after oral exposure, however observations in humans are very limited.

Fenbendazole is not expected to have a skin or eye irritating potential at concentrations up to 10%, although, in the final formulation fenbendazole is present at a concentration of 20%. It is considered unlikely that the final formulation will have skin or eye irritating/damaging effects.

The skin sensitising property of fenbendazole in the final formulation is unknown.

The warnings and safety measures are identical to previously accepted for Panacur AquaSol (pigs). In addition, a warning sentence with respect to handling of the product by pregnant women has been included in the SPC. As the applicant intends to have a combined packaging for Panacur AquaSol for pigs and chicken, the applicant already provided the combined SPC and labelling which contains the additional information.

Based on the data provided the ERA can stop at Phase I. Panacur AquaSol is not expected to pose a risk to the environment when used according to the SPC.

Residues documentation

Identification of the product concerned

The residue study for meat and eggs was performed with Panacur AquaSol 200 mg/ml drinking water suspension for chicken (wet-milled formulation), containing the active substance fenbendazole (200 mg/ml) and excipients benzyl alcohol (20 mg/ml), polysorbate 80, simethicone emulsion 30% and purified water (q.s. to 1 ml).

Residue studies

Tissues:

Residue depletion study was performed with the commercial formulation. Animals (layers: Lohmann Braun; m+f; 26 weeks at slaughter; bw: 1.530–2.654 kg and broilers: Ross 308; m+f; 10 weeks at slaughter; bw: 3.338–4.653 kg; 12 animals per slaughter group) were dosed 1 mg fenbendazole/kg bw/day for 5 consecutive days. Panacur AquaSol was administered via drinking water given for voluntary up-take (drinkers: container + drinker dish) during 6 hours. The concentrations of fenbendazole in the medicated water were determined based on the nominal daily dose of fenbendazole (1 mg/kg bw), the bodyweight of the heaviest bird per production type (heaviest layer: 2.654 kg, heaviest broiler: 4.653 kg) and the average volume of water consumed by the birds during 6 hour assessment periods (average volume consumed by 24 layers: 2.748 l, average volume consumed by 24 broilers: 6.783 l).

Animals were sacrificed at 24, 48, 72, 96 and 120 hours after completion of consumption of the

medicated drinking water on the last day of dosing. Liver, kidneys, skin+fat and muscle (breast) samples were collected and stored at approximately -80°C until analysis (storage stability was guaranteed for the storage period). Residue concentrations of the marker residue were determined using the routine analytical methods (HPLC (high-performance liquid chromatography) with fluorescence detection) and matrix matched calibration. Limit of quantification (LOQ): $25\ \mu\text{g}/\text{kg}$ for all tissues. QC-samples (fortified broiler and layers matrices) were within the acceptable limits.

Eggs:

Residue depletion study was performed with the commercial formulation. Animals (Lohmann Selected Leghorn and Lohmann Brown; bw: 1.367–2.314 kg; age: 27 weeks at start).

Twenty birds (eggs of 12 hens were collected) were dosed $1\ \text{mg fenbendazole}/\text{kg bw}/\text{day}$ for 5 consecutive days. Panacur AquaSol was administered via drinking water given for voluntary up-take (one drinking bottle per pen, i.e. 2 layers) during 6 hours. The concentration of fenbendazole in the medicated water was determined based on the nominal daily dose of fenbendazole ($1\ \text{mg}/\text{kg bw}$), the bodyweight of the heaviest bird (heaviest layer: 2.314 kg) and the average volume of water consumed by the birds during 6 hour assessment periods (average volume consumed by 2 layers: 0.258 l).

The eggs laid (minimum of 10 eggs per sampling time) by the hens on the day before the first administration and up to 12 days after the last administration were collected and homogenised. Samples were homogenised (full albumen and yolk) and stored at approximately -80°C until analysis (storage stability was guaranteed for the storage period). Residue concentrations of the marker residue were determined using the routine analytical method (HPLC with fluorescence detection) and matrix matched calibration. LOQ: $100\ \mu\text{g}/\text{kg}$. QC-samples were within the acceptable limits.

Pharmacokinetics

Fenbendazole suspension is quickly absorbed. The metabolic pathway of fenbendazole in chickens is the same as in mammals. It is metabolised to oxfendazole, and further sulfoxidated to oxfendazole sulfone. Liver appears to be the target tissue, followed by kidney, skin+fat and muscle. No information is provided on the extent of absorption, plasma protein binding or whether the product is mainly excreted via the kidney or via faeces. Though in the MRL summary report for fenbendazole (EMA/MRL/866/03-FINAL) it can be found that elimination of fenbendazole is predominantly by the faecal route.

Residue levels in laying hens are higher when compared to broilers. In eggs the highest residues are found one day after last treatment, thereafter, total residue concentrations declined rapidly.

Fenbendazole was found in eggs only whereas oxfendazole and oxfendazole sulfone were found in all tissues and eggs.

Depletion of residues

In all edible tissues, the maximum concentration of fenbendazole residues (i.e. the marker residue oxfendazole sulfone) was observed at the first slaughter time point (24 hours after the last administration). The highest concentrations were observed in liver tissue. Thereafter, the residue concentrations declined quite rapidly in all tissues.

All residue levels were below the MRL of the respective tissue at 72 hours (liver), 96 hours (muscle) and 120 hours (kidney and skin+fat).

In eggs all residue levels were below MRL at all-time points (i.e. during and after treatment).

MRLs

The active substance, fenbendazole, is included in table 1 of the Annex of Regulation EU No. 37/2010.

Pharmacologically active substance	Marker residue	Animal species	MRL (µg/kg)	Target tissues	Other provisions
Fenbendazole	Sum of extractable residues which may be oxidised to oxfendazole sulfone	All food producing species except fish	50 50 500 50 10 1300	Muscle Fat Liver Kidney Milk Eggs	For porcine and poultry species the fat MRL relates to "skin and fat" in natural proportions

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

Withdrawal periods

Based on the provided residue depletion study in tissues a withdrawal period of 6 days for edible tissues can be established for Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken when administered at the maximum recommended dose of 1 mg fenbendazole/kg bw/day for 5 consecutive days.

The withdrawal period for slaughter is calculated using the alternative approach by taking the first time point where all concentrations are below the respective MRL (72 hours for liver, 96 hours for muscle and 120 hours for kidney and skin+fat) and adding a safety span of 20%, resulting in a withdrawal period of 4 days for liver, 5 days for muscle and 6 days for kidney and skin+fat. Overall withdrawal period for slaughter: 6 days.

Based on the provided residue depletion study in eggs a withdrawal period of zero days for eggs can be established for Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken when administered at the maximum recommended dose of 1 mg fenbendazole/kg bw/day for 5 consecutive days.

As at all-time points residue levels were below MRL (though above LOQ), the withdrawal period is calculated by estimating the 95% tolerance limit for each time point (safe concentration per milking (SCPM) method for milk). The 95% tolerance limits for all time points were below MRL. Withdrawal period for eggs: zero days.

Analytical methods

The residue depletion studies including their analytical methods have already been evaluated for the purpose of extending the fenbendazole tissue MRLs to chickens. The analytical methods were considered to be sufficiently validated. Validation parameters were within the limits set out in Volume 8 of the publications 'The rules governing medicinal products in the European Union'.

For tissues accuracy and precision was determined at concentrations of 25, 200 and 1,000 µg/kg; for

eggs, at concentrations of 100, 1,000 and 2,500 µg/kg. Both within-run and between-run accuracy were within the –30% and +10% range for all tissues and eggs. The coefficient of variation values were less than 20%. The limit of detection was respectively 3.31, 4.95, 4.83, 3.43 and 22.20 µg/kg for muscle, liver, kidney, skin+fat and eggs. The LOQ was 25 µg/kg for all tissues and 100 µg/kg for eggs.

Stability of incurred residues (including eggs) in storage at –20 °C (–80 °C for skin+fat) was shown for at least 2 months.

Overall conclusions on the residues documentation

The provided studies investigated the depletion of fenbendazole residues in tissues and eggs after administration of a fenbendazole suspension formulation to chicken at the recommended dosage regimen.

Based on the provided residue depletion studies a withdrawal period of 6 days for slaughter and zero days for eggs can be established for Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken when administered at the maximum recommended dose of 1 mg fenbendazole/kg bw/day for 5 consecutive days.

Part 4 – Efficacy

Pharmacodynamics

Fenbendazole belongs to the group benzimidazole anthelmintics, which acts by disruption of the microtubule function via direct binding to parasite tubulin monomers, with beta-tubulins being the primary benzimidazole target. Microtubules are major components of the mitotic spindle of eukaryotic cells, and in some cells, they form the cytoskeleton (i.e. brain cells). Fenbendazole also interferes with the energy metabolism and cellular homeostasis of the worm.

Both adult and immature stages of gastro-intestinal nematodes are affected. In general, benzimidazoles show a selective toxicity for helminths, whereas they are well tolerated in mammals. This selective toxicity is due to a more stable bond of the fenbendazole-tubulin monomer complex in helminths compared to mammals (Lacey (1990); Lacey (1987), McCracken and Stillwell (1991), Gill and Lacey (1992) (G.J. Russell, et.al. Biochemical pharmacology (1992) 43: 1095-1100). Target animal safety studies revealed that chickens tolerate fenbendazole well at up to 5x the recommended dose.

Development of resistance

One literature study was submitted. In this study resistance of *Trichostrongylus* spp. in wildlife birds was investigated. These worms are not included in the current indication.

The development of nematode resistance to benzimidazoles has become a significant problem, but so far not in the chicken.

The risk for resistance development cannot be excluded, but will not be higher for Panacur AquaSol, compared to in-feed medication of fenbendazole when the appropriate measures are taken to exclude the presence of *Capillaria* spp. infestations. A suitable contraindication stating that the product should not be used in case of infestation with *Capillaria* spp., and a warning stating that frequent and

repeated use of any anthelmintic could increase the risk for development of resistance is included in the SPC.

Pharmacokinetics

Fenbendazole will be absorbed from the gastro-intestinal tract after oral administration. The extent of absorption differs among species. In chickens the oral bioavailability of fenbendazole was 16% when administered in Panacur AquaSol suspension according to Petersen and Friis (2000) and Davis et.al (1988),. When fenbendazole is formulated as Panacur AquaSol the bioavailability increases according to a submitted GLP (good laboratory practice) bioequivalence study. Fenbendazole and its metabolites are distributed throughout the body and the highest concentrations are found in the liver (Heggem, 2008,). Fenbendazole is rapidly metabolised by liver microsomes. The first metabolite is oxfendazole, which results from sulfoxidation. This metabolism step is reversible. Oxfendazole is further sulfoxidated to oxfendazole-sulfone. The major metabolites are excreted in bile (Short et al. 1988a, literature study). Fenbendazole can also be demethoxycarbonylated to fenbendazole amine or hydroxylated to p-hydroxyfenbendazole (Short, 1988, literature study). A residue study with radiolabeled fenbendazole showed that the metabolic pathway of fenbendazole in chickens is the same as in mammals.

Dose determination/justification

All studies were conducted under GCP (good clinical practice) conditions. Three dose determination studies have been conducted and three dose confirmation studies. In all studies, both clinical and field studies, the dosage of 1 mg fenbendazole/kg bw for 5 consecutive days gives a reduction greater than 90% of adult *Ascaridia galli* and *Heterakis gallinarum* in geometric mean adult worm counts which is sufficient according to VICH GL7 and GL21. However, all studies (see table) were performed using naturally infected chickens and not in all studies this infection could be considered adequate according to the statistical analysis or according to the recommendation of VICH GL21.

Percent (%) efficacy worm/larval counts

Dose (study)	Treatment duration (days)	<i>A. galli</i> L5+ Adult/L4	<i>Capillaria</i> spp. L5 +Adult/L4	<i>H. gallinarum</i> L5+adult/L4
1 mg/kg	5	97.9/85.6	53.1/1.3	99.8/87.7
1 mg/kg	5	97.3/10.3	4.9/20.3	96.9/69.2
1 mg/kg	5	93.9/-17.3	11.3/35.0	97.3/-12.4
1 mg/kg	5	100	80	93
1 mg/kg	5	98.7	23	99.2
1 mg/kg	7	99.6/65.6	37.5/-17.5	99.6/70.97
1 mg/kg	7	100*	-6.9	100
2 mg/kg	5	100/100	93.3/74.1	100/100
2 mg/kg	5	100/55.6	66.6/72.7	99.3/92.4
2 mg/kg	5	100/48.2	68.9/87.9	99.9/75.2
2 mg/kg	5	100*	96.3	100
2 mg/kg	5	100**	98.1	99.4
2 mg/kg	5	100	92.1	92.1
3 mg/kg**	5	100**	99.4	99.5
3 mg/kg*	5	100*	95.3	100
3.3 mg/kg**	3	100**	94.2	100

3.5 mg/kg	3	100/71.9	66.6/72.7	99.4/93.9
3.5 mg/kg	3	98.5/50.1	50.8/54.6	99.4/90.4
5 mg/kg) **	1	89.8	59.4	74.3
10 mg/kg	1	100	85.7	97.4
15 mg/kg	1	100	91.5	98.2

Efficacy \geq 90%, which is sufficient according to the VICH GL7.

* Study: The natural *A. galli* infection was not adequate according to the statistical analysis and adult stages were investigated not L5. Only efficacy against adult stages is written down.

** : Chickens were not adequately infected with larval stages and *A. galli*. Only efficacy against adult stages is written down

It can be concluded that 1 mg/kg fenbendazole/kg bw/day for 5 consecutive days leads to sufficient efficacy in worm count reduction against L5+adult stages of *Ascaridia galli* and *Heterakis gallinarum* however this dose is suboptimal for *Capillaria* spp.

This might form a risk of resistance development of *Capillaria* species, the most virulent nematode in chickens. Therefore in the SPC a statement was added that in case of *Capillaria* infections the efficacy of the veterinary medicinal product at the recommended dosage is not sufficient for the treatment of infections with *Capillaria* spp. In case of *Capillaria* infestation another appropriate anthelmintic veterinary medicinal product has to be used. A contraindication has been added to the SPC 'Do not use in case of *Capillaria* spp. infestations'. The product can be used in outdoor chicken.

In conclusion, the current dosage is sufficient for adult (and L5 stage) of *Ascaridia galli* and *Heterakis gallinarum* but not sufficient for larval stages (L3 or L4) of these worms. Also *Capillaria* spp. require a higher dose of fenbendazole to achieve sufficient efficacy and this product is contraindicated in case of *Capillaria* infestations in flocks.

Target animal tolerance

Two studies have been conducted, testing 1x, 3x and 5x the recommended dose of the test article for 15 consecutive days. The first study used growing broilers, aged 3 weeks at the start of the study. Growing broilers tolerated the 20% fenbendazole suspension (marketed as Panacur AquaSol) well. The second study used 30-week-old female layers. The oral administration of 20% fenbendazole suspension in drinking water at dose levels of 1x, 3x and 5x the recommended dose for 15 consecutive days was well tolerated in the laying hen. Of all investigated egg parameters no adverse events were noted except for egg weight that was significantly lower (1.2 gram) in the highest two treatment groups (3x and 5x the recommended dose) compared to the control group in the second half of the treatment period. However, intra-individual variance of egg weight between days could be considerably larger. In field studies this parameter was not evaluated and therefore it is unknown if this effect was coincidental.

In addition a reproductive safety study in compliance with GLP has been conducted in broiler breeders, testing 3x the recommended dose for 21 consecutive days. The results from the study demonstrated that the use of the product at this higher dose (3 mg/kg/day for 21 days) had no treatment related adverse effect on parameters observed relating to the safety of reproducing chicken and their offspring.

In the field, using breeders, no observations have been performed on the hatched chicks (bodyweight, quality).

No adverse events, by daily observation on chickens, were noted in dose determination/finding studies as well as in field studies. The youngest treated animals were 3-week old.

Field trials

Two field trials have been conducted. The first trial included six herds of breeders in 3 countries (The Netherlands, France and Italy). The study included both layer breeders and broiler breeders. Worms were counted in 15 animals before start of treatment and a post-treatment worm count was conducted in 15 chickens 7 days after the end of treatment period. The overall efficacy against adult *A. galli* (90.80%) and *H. gallinarum* (98.34%) with a daily dosage of 1 mg/kg bw on 5 consecutive days is sufficient according to VICH GL7 (> 90%). Post-treatment L5 counts, conducted 6 days after end of treatment period, were compared to pre-treatment L5 counts. The population of L5 larvae is not a static population but is an intermediate stage between L4 larvae and adult worms. The current dose of fenbendazole 20% w/v solution has insufficient efficacy against L4 larvae of *A. galli*, resulting in development of large amounts of L5 larvae in the post-treatment sample of one site (layer breeders). This resulted in an efficacy < 90%, which is insufficient. Thus in the SPC: 'control of *A. galli*/*H. gallinarum* infection' has been deleted from the indication. L4 larvae of *A. galli* are not included in the indication. No test article related adverse events were noted during daily observations. In two sites the number of laid eggs decreased slightly more (2%) during treatment than expected according to the standard (Ross standard), however, numerous factors could be of influence.

The second study included one site with replacement layers (Italy). In this study the birds were naturally infected with *A. galli* and it was not possible to demonstrate adequate infection using a statistical approach, therefore this study is not discussed any further.

Overall conclusion on efficacy

The current dose of 1 mg fenbendazole/kg bw/day, administered for 5 consecutive days, is effective against L5 and adult *Ascaridia galli* and *Heterakis gallinarum* worms according to VICH GL7 and GL21. However it is a suboptimal dose for treatment of *Capillaria* species and L3/L4 larval stages of *A. galli* and *H. gallinarum* and the product is not indicated for these infestations.

Part 5 – Benefit-risk assessment

Introduction

This application is for an extension to add a new target species to an already authorised product, Panacur AquaSol indicated for the treatment and control of gastro-intestinal nematodes in pigs.

This extension application concerns the use of Panacur AquaSol in a new target species, chickens. Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken is identical to Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for pigs in all aspects of formulation, manufacture, control testing, type of packaging and pack sizes.

The proposed indication is: *Treatment of gastro-intestinal nematodes in chicken infected with Ascaridia galli (L5 and adult stages); Heterakis gallinarum (L5 and adult stages).*

Panacur AquaSol is a white to off-white oral suspension (20% w/v) for use in drinking water containing 200 mg/ml fenbendazole as active substance, benzyl alcohol as preservative, and polysorbate 80, simethicone emulsion 30% and purified water as other excipients.

Benefit assessment

Direct therapeutic benefit

The proposed dose of 1 mg fenbendazole/kg bw/day, administered for 5 consecutive days, is effective in chickens against L5 and adult *Ascaridia galli* and *Heterakis gallinarum* nematodes, in compliance with VICH GL7 and GL21. The therapeutic benefit for the animal, i.e. efficacy is > 90%.

Additional benefits

An additional benefit of this product is that fenbendazole is formulated in a suspension with the wet milling technique employed and therefore enables treatment via drinking water to chickens.

Risk assessment

The formulation and the manufacture of Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken is identical to Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for pigs which is well described and specifications set ensure that a product of consistent quality is produced.

The main potential risks are the following:

For the target animal:

The product appears to be well tolerated when administered to the target species as recommended.

For the user:

It is not expected that the product will pose an unacceptable risk to the user when used in accordance with label recommendations. The user safety assessment concluded that oral and dermal exposure to the product may give rise to adverse reactions and appropriate risk mitigation measures are included in the SPC (and other product information).

For the environment:

It is not expected that the product will pose a risk to the environment when used according to the SPC.

For the consumer:

Based on the provided residue depletion studies a withdrawal period of 6 days for slaughter and zero days for eggs can be established for Panacur AquaSol 200 mg/ml oral suspension for use in drinking water for chicken when administered at the maximum recommended dose of 1 mg fenbendazole/kg bw/day for 5 consecutive days.

Specific potential risks:

Concerning emergence of resistance, the current dose of 1 mg fenbendazole/kg bw/day, administered for 5 consecutive days, is a suboptimal dose for treatment of *Capillaria* species and L3/L4 larval stages of *A. galli* and *H. gallinarum*. The potential risk of resistance development is addressed by adding a contraindication to the SPC, that in case of a proven *Capillaria* infestation another appropriate anthelmintic veterinary medicinal product has to be used.

Risk management or mitigation measures

Appropriate warnings have been included in the SPC to inform on the potential risks to the target animals and the user and the environment and to provide advice for reducing these risks.

The product information contains a contraindication to prevent use of the product in case of a proven *Capillaria* infestation.

In light of the extension of the indication to a new target species, it is recommended to re-start the PSUR (periodic safety update report) cycle for Panacur Aquasol to ensure more frequent pharmacovigilance monitoring. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 30 June 2014.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the indication for the treatment and control of gastro-intestinal nematodes in chickens.

The formulation and manufacture of Panacur AquaSol is well described in the original application for pigs and specifications set will ensure that product of consistent quality will be produced.

Panacur AquaSol is well tolerated by the target animals. When used as recommended, and taking into account risk mitigation measures indicated in the SPC, the use of the product is not expected to pose an unacceptable risk to the environment or to the user.

An adequate withdrawal period in chickens has been set.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Panacur Aquasol for 'Treatment of gastro-intestinal nematodes in chicken infected with *Ascaridia galli* (L5 and adult stages); *Heterakis gallinarum* (L5 and adult stages)' are considered to be in accordance with the requirements of Directive 2001/82/EC. The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and other product information.