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CVMP assessment report
Panacur AquaSol (EMEA/V/C/2008)

Common name: Fenbendazole

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

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Introduction

An application for the granting of a community marketing authorisation of Panacur AquaSol has been submitted to the Agency on 28 September 2010 by Intervet International BV in accordance with Regulation (EC) No. 726/2004. Eligibility under Article 3(2)(b) of Regulation (EC) No 726/2004 as a significant technical innovation was confirmed in view of the fact that Panacur AquaSol uses an innovative manufacturing process combined with a unique formulation such that the 20% fenbendazole suspension forms a physically stable and homogeneously distributed product for administration via drinking water.

Panacur AquaSol contains fenbendazole as the active substance and is presented in packs/containers of 1 bottle in three different sizes 125 ml, 1 litre and 4 litres. It is indicated for the treatment and control of gastro-intestinal nematodes in pigs. The route of administration for this oral suspension is in-drinking water use. The target species are pigs.

Part 1 - Administrative particulars

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the pharmacovigilance system (DDPS). The information presented demonstrate that the applicant has in place a pharmacovigilance system that will allow it to comply with its legal requirements in respect of pharmacovigilance.

Manufacturing Authorisations and Inspection Status

Valid manufacturing authorisations are in place for each site in the EU/EEA carrying out manufacture of the product, packaging and batch release. Any additional inspection of these sites was not considered necessary.

Testing

An annual sampling and testing programme for centrally authorised products is conducted in accordance with Art. 57(r) of Regulation (EC) 2004/726 in conjunction with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Official Medicines Control Laboratories of the EU/EEA Member States. For Panacur AquaSol no specific final product testing was recommended. The selection of products for inclusion in any annual sampling and testing programme is largely driven through a risk based approach.

Part 2 - Quality

Composition

The proposed veterinary medicinal product is an oral suspension for use in drinking water containing 200 mg/ml fenbendazole as the active substance, benzyl alcohol as preservative, polysorbate 80 as surfactant, simethicone emulsion 30% as an anti-foaming agent and purified water as excipients. The excipients all comply with the European Pharmacopeia (Ph.Eur.) apart from simethicone which complies with the USP.

The same formula has been used for clinical studies and user trials.

Container

Panacur AquaSol is filled into containers made of natural high density polyethylene (HDPE). The containers are sealed with a pulp board/aluminium/polyester/medium density polyethylene (MDPE) (in contact with the suspension) thermoseal and closed with a child resistant screw cap made of polypropylene.

Three pack sizes are filled: 125 ml, 1 litre and 4 litres. The 4 litre container is provided with a separate tap/dispenser.

Development pharmaceutics

Since fenbendazole is practically insoluble in water, the possibility was investigated of solubilising the drug by various means, but none of these provided sufficient solubility.

Therefore, the objective was to develop a suspension of 20% w/v fenbendazole to be administered via drinking water as homogeneous medicated water. The product had to ensure an accurate dosing and avoid any blocking of the equipment commonly used for medication via drinking water.

This was achieved by using an extreme degree of size reduction. The resistance of such suspensions to sedimentation in comparison with conventional and micronised suspensions has been demonstrated and confirmed in actual field studies.

To facilitate wetting of the particles during manufacture the surfactant polysorbate 80 was selected and its inclusion level optimised on the basis of further sedimentation studies. To prevent foaming during manufacture the antifoaming agent simethicone is included at the recommended level. Since the product is an aqueous preparation for multidose use, a preservative is also required. As a result of preservative efficacy testing benzyl alcohol was found to be the most effective preservative.

Considering that the finished product is not light sensitive, natural HDPE containers were chosen as the primary packaging.

The required small particle sizes can only be achieved by wet milling and the applicant has studied this process in detail. Scale-up trials were conducted in a logical progression from laboratory to pilot to manufacturing scale. The milling process is capable of producing a suspension of consistently reproducible particle size.

Method of manufacture

The manufacturing process is relatively straightforward, consisting of mixing and milling of the ingredients and was sufficiently described: a concentrated fenbendazole suspension is prepared and passed through a bead mill. After further milling and mixing with the remaining excipients the suspension is filled into containers.

Validation on production-scale batches indicates that the manufacturing process yields a robust product. Since the manufacture of a suspension is considered a non-standard process, the applicant has submitted validation results of full-scale batches. Based on the results obtained for these batches during the validation of the process it can be concluded that the applied manufacturing process using the wet milling steps leads to a final product that consistently meets the set specifications. Furthermore a holding time between transfer and filling has been established.

Control of starting materials

Active substance

Fenbendazole is an existing active substance, described in the Ph. Eur. Full information is included in the dossier. The synthesis has been described in sufficient detail. The starting materials are acceptable. The process is validated based on three full-scale batches. The control of impurities in the active substance is considered appropriate. A re-test period of 3 years without specific storage conditions, is accepted based on submitted real-time and accelerated stability results.

Excipients

For benzyl alcohol, polysorbate 80 and purified water reference is made to the Ph. Eur. For simethicone emulsion 30% reference is made to the USP. These references are appropriate. Additional tests are not required for this application.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Declarations on absence of TSE suspicious material have been provided by the active substance manufacturer and the drug product manufacturer. None of the ingredients used in the product are of human or animal origin. Declarations to this effect from each of the excipient suppliers are provided. The finished product is compliant with the Note for Guidance for minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 October 2003).

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed at release and during shelf life are appropriate to control the quality of the finished product. Specifications have been set for description, identification of fenbendazole, identification of benzyl alcohol, content of active substance and related substances, content of benzyl alcohol, manufacturing related impurities, particle size distribution, resuspendability and sedimentation after resuspendability, filling volume and microbial limit test. All control methods are suitably described and sufficiently validated. Results of batch analysis of full-scale batches confirm compliance to the proposed specifications.

Stability

The stability data submitted regarding the finished product substantiate the proposed shelf life of 24 months without specific storage condition. Stability studies on photostability demonstrated that the finished product is not light sensitive. Stability studies on freeze–thaw cycles demonstrated that the suspension shall not be frozen. Stability after first opening of the container and stability of medicated water was demonstrated for the proposed 6 months and for 24 hours respectively.

Overall conclusions on quality

The chosen formula as presented in the dossier has been used for clinical studies and user trials.

The dossier provides a suitable description of the active substance and the chosen formulation, and demonstrate that production leads to a product of consistent quality. In general the specifications for the active substance and the finished product are suitable. The analytical methods are well described and data of their validation confirm their suitability. Stability studies have been performed according to VICH guidelines. The primary stability studies are on-going. The stability studies done on the active substance allow a re-test period of 36 months, without specific storage conditions. In view of the stability data provided, the proposed shelf life of 24 months for the finished product is acceptable.

Part 3 – Safety

The safety of fenbendazole has been studied and described in detail.

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.

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 animals species.

Pharmacokinetics

Comparative studies between the old and new formulations of fenbendazole were performed which showed an increase in bioavailability for the smaller particle size. Otherwise the pharmacokinetic behaviour was comparable.

Due to its poor solubility, absorption of orally administered fenbendazole from the GI tract is limited. For the pig the absolute oral availability is about 27%.

After absorption, fenbendazole is rapidly metabolised, the major metabolite being the sulfoxide oxfendazole. Oxfendazole itself is further sulfoxidated to oxfendazole sulfone. Fenbendazole accounts for less than 10% of the total AUC0-LOQ, oxfendazole for about 2/3.

Other metabolic pathways are also known (demethoxycarbonilation; hydroxylation) resulting in FBZ-amine or p-hydroxyfenbendazole.

Several studies were conducted to compare the oral availability of Panacur AquaSol with the oral availability of fenbendazole from premix formulations.

In 4 studies the pharmacokinetic characteristics of Panacur AquaSol (dose range: 2, 2.2, 2.5, 3, 5 and 6 mg/kg bw) were compared to those of a conventional 4% powder formulation (dose: 5 mg/kg bw) and a 20% premix formulation (doses: 3 and 9 mg/kg bw).

With respect to Cmax and AUC0-LOQ Panacur AquaSol at a dose of 2.2 mg/kg was considered equivalent to the 20% premix 3 mg/kg, using AUC0-loq values for fenbendazole.

On average the availability of the Panacur AquaSol formulation is about 30% higher compared to the conventional 4% powder formulation and the 20% premix.

The absolute oral bioavailability of fenbendazole, administered as a conventional 4% powder formulation suspended in water at a dose rate of 5 mg/kg, was about 27%, when compared to a dose of 1 mg/kg by the intravenous route.

Since the relative availability of Panacur AquaSol was about 30% higher, the absolute availability was calculated to be about 35%.

Toxicological studies

Fenbendazole, the active substance contained in Panacur AquaSol, is a well-established substance that has been widely and safely used for more than 30 years. Therefore, the applicant refers to published, valid safety assessment of fenbendazole including the CVMP MRL summary report EMEA/MRL/193/97-FINAL.

An extensive literature search on the toxicity and safety of fenbendazole covering the last 10 years did not provide new relevant information on the toxicity of fenbendazole.

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.

Comparative studies between the old and new formulations of fenbendazole were performed which showed an increase in bioavailability for the smaller particle size. The CVMP accepted that the toxicological studies conducted with the old formulation were applicable to this product.

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 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

Fenbendazole is considered well tolerated by pigs. Using conventional formulations, doses up to 2000 mg/kg bw have been administered to pigs for 14 days without producing clinical signs or histopathological changes.

Furthermore, fenbendazole has been used in practice for over 35 years and pharmacovigilance data have been produced since 2000. Via the pharmacovigilance system only a few cases were reported in relation to fenbendazole use, but no case was classified as " possible".

Data indicate that the margin of safety of fenbendazole for the pig is wide. Even the higher availability of Panacur AquaSol is not likely to affect the width of this margin.

The excipients are commonly used substances in authorised pharmaceutical formulations for veterinary use. Their use is considered safe.

Reproduction safety in the target species has been studied separately. No adverse effect on male and female fertility or offspring was demonstrated.

Reproductive toxicity

The MRL summary report describes 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 showed no evidence of foetotoxicity or teratogenicity in rats, but for rabbits, a NOEL 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 is practically non-irritating to the skin and eyes. Fenbendazole is not a skin sensitiser when tested in a 10% formulation in guinea pigs.

User safety

Hazard characterisation

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

In vivo, fenbendazole mainly exists in its oxidised oxfendazole form. The ADI for fenbendazole has been adopted from oxfendazole. This ADI of 7 µg/kg bw per day was established by applying a safety factor of 100 to the NOEL of 0.65 mg/kg bw per day for hepatic vacuolation seen in a carcinogenicity study in rats treated with oxfendazole. A 30-day study in rats revealed a NOAEL of 2500 mg/kg (highest dose tested), a 90-day dog study revealed a NOAEL of 125 mg/kg (highest dose tested).

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 2000 mg per person were reported to cause no adverse effects.

Adverse effects on reproduction and/or development cannot be excluded for fenbendazole. From a 3-generation study a NOEL of 15 mg/kg was derived (based on reductions in fertility, survival and growth of the neonates during lactation; parental animals had diarrhoea, reduced body weight gain and pathological changes in the liver). From a teratogenicity study in rabbits a NOEL of 25 mg/kg bw/day was derived (based on an increase in delayed ossification).

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

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%.

The skin sensitising property of fenbendazole in the final formulation is unknown, however any safety concern related to sensitisation has been covered by the proposed risk management measures.

The excipients are considered to be of low toxicity after systemic exposure, though may be harmful after ingestion or inhalation. Skin and/or eye irritation may occur. Also, hypersensitivity reactions have been reported.

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 1561 mg per person (i.e. 26 mg/kg bw). As no dermal bioavailability data are available for the suspension, a very worst case bioavailability of 100% was used 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 safety measures are proposed which would normally be acceptable for formulations with sensitising properties, i.e. the wearing of gloves. 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. 2500 mg/kg bw derived from the 30-day rat study, 125 mg/kg bw derived from the 90-day dog study). To estimate the internal NOAEL, an oral bioavailability of 27% (in 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 Exposures are 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 (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 2 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, which is the very worst case scenario.

Uptake through intact skin would probably not be higher than uptake through the GI tract.

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 that contaminated clothes should be removed after spillage.

For effects on foetuses (delayed ossification), the calculated margin of exposure is only 3 (even wearing gloves), which is normally regarded as being too low. However, since the exposure estimate is very worst case, and the delayed ossification (reflecting growth retardation) would most likely require daily exposures for a longer period of time (the product posology includes only a 2-day treatment), the actual margin of safety is probably much higher. Therefore, pregnant women can also handle the product safely, when the safety precautions mentioned in the SPC are followed.

Environmental risk assessment

For the phase I risk assessment, the decision tree has been followed according to VICH guideline GL6 (CVMP/VICH/592/98-FINAL). The smaller particle size does not influence the phase I risk assessment. None of the questions 1-6 and 14 allowed for a stop in phase I and a PECsoil has been calculated for question 17. The calculated PECsoil values were 43.44 µg/kg, 29.47 µg/kg and 10.46 µg/kg for weaner pigs, fattening pigs and sow+litter respectively. Therefore it can be concluded that the initial predicted environmental concentration in soil ($PEC_{soil, initial}$) for fenbendazole is lower than 100 µg/kg. A phase II assessment is not considered necessary.

Appropriate warnings are included in the SPC to address spillage of the product were this to occur and to avoid release into water courses as this may be dangerous for aquatic organisms.

Overall conclusions on the safety documentation

Fenbendazole is known for its wide safety margin in pigs and other animal species for many decades. Therefore no new safety studies in pigs have been performed with Panacur AquaSol but a review of available safety studies and pharmacovigilance case reports of fenbendazole in pigs has been performed.

Based on the actually generated data fenbendazole is well tolerated in pigs, irrespective of the sex, age and reproductive status of the animals. During the clinical trials conducted with the final formulation, the product was well tolerated with no adverse effects observed.

Only one animal showed cardiovascular symptoms which were considered to be non product related. No adverse reactions are expected at the intended dosing regime and corresponding drug level.

Fenbendazole has been used safely in breeding sows and boars. Overdoses up to 10 times the recommended doses were well tolerated. Adverse effects have not been observed.

No contra-indications or special precautions for target animals are included in the SPC.

The product can be handled safely by users wearing gloves.

The product is not expected to pose a risk for the environment when used as recommended.

Residues documentation

Identification of the product concerned

The residue study was performed with Panacur AquaSol 200 mg/ml drinking water suspension for pigs. containing the active substance fenbendazole (200 mg/ml) and excipients benzyl alcohol, polysorbate 80 simethicone emulsion 30% and purified water. The particle size used in the residue study was provided and 90% of the particles were smaller than 400 nm.

Residue studies

The GLP-compliant residue study was performed with a 20% fenbendazole suspension. The chemical composition is equal to that of the final formulation, i.e. "Panacur Aquasol 200 mg/ml drinking water suspension for pigs". The particle size distribution of the 20% fenbendazole suspension used in the residue depletion study was 90% < 400 nm. During shelf life the particle size and distribution may slightly change. This however is not supposed to affect the residue behaviour of "Panacur Aquasol 200 mg/ml drinking water suspension for pigs" in a negative manner, it may even be more favourable (i.e. results in lower residues) than the residue behaviour of the fenbendazole suspension used in the residue depletion study.

Thirty healthy pigs (15 castrated males and 15 females) of a commercial breed (Pietrain x "Deutsche Hybridschwein", a German hybrid race) were included in the study and randomly allocated to 4 groups of 6 animals (3 females and 3 castrated males) and 6 reserve pigs. The bodyweight of the pigs used in the study is representative for slaughter pigs (about 100 kg). Breeding pigs (about 250 kg) were not investigated. Since the dosage for medicated water is expressed on a bodyweight basis, this is acceptable.

A calculated average dose of 2.3 mg fenbendazole/kg bw/day was consumed by the pigs which is slightly less than the recommended dose of 2.5 mg fenbendazole/kg bw/day. Nevertheless, the 3 day treatment represents an overdose with regards to the currently proposed dosing scheme (2x 2.5 mg/kg bw/day). As a result of this overdose, the derived withdrawal periods from this study will probably be longer than necessary for a 2 day dosing scheme.

One group each was slaughtered at 24, 48, 72, 98 hours after the medicated drinking water was consumed entirely on the last administration day. The tissue samples (skin with fat, muscle, liver, kidneys) were analysed within the validated stability period. Fenbendazole residues were quantified in these tissue samples using a validated HPLC method with fluorescence detection (reported LLOQ 25 µg/kg for each tissue). Fenbendazole residues (sum of parent, oxfendazole and oxfendazole sulfone) were oxidised to and expressed as oxfendazole sulfone. The performance of the method at the time of analysis of the samples was considered acceptable.

Pharmacokinetics

Fenbendazole suspension is quickly absorbed. It is metabolised to oxfendazole, and further sulfoxidated to oxfendazole sulfone. Liver appears to be the target tissue, followed by kidney, fat+skin and muscle. Fenbendazole and its metabolites are rapidly cleared from the plasma and are below 10 ng/ml within 72 hours after administration. No information is provided on the extent of absorption, plasma protein binding or whether the product is mainly excreted by urine or faeces. Though in the MRL summary report for fenbendazole (EMEA/MRL/866/03-FINAL) it can be found that elimination of fenbendazole is predominantly by the faecal route.

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 (range: 1555-8187 µg/kg).

Thereafter, the residue concentrations declined quite rapidly in all tissues. The residue concentration range in liver at 48h was 66 to 837 µg/kg and below 25 µg/kg-33 µg/kg at 72h.

Ninety six hours after the last administration all residue concentrations in all animal tissues were below the LOQ of 25 µg/kg.

MRLs

The active substance, fenbendazole, is included in table 1 of EU Regulation No. 37/2010. *In vivo*, fenbendazole mainly exists in its oxidised oxfendazole form. But as fenbendazole, oxfendazole and oxfendazole sulfone are detectable in edible tissues, the sum of extractable residues which may be oxidised to oxfendazole sulfone is used as marker residue (EMEA/MRL/866/03-FINAL, 2004).

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Fenbendazole	Sum of extractable residues which may be oxidised to oxfenda-zole sulphone	All ruminants, porcine, *Equidae*	50 µg/kg 50 µg/kg 500 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions'.	Antiparasitic agents/Agents against endoparasites
		All ruminants	10 µg/kg	Milk		

The MRL status of the excipients of the product "Panacur Aquasol 200 mg/ml drinking water suspension for pigs" is indicated in the following table:

Excipient	MRL status
benzyl alcohol (E1519)	Table 1 of Annex to EU Regulation No 37/2010 no MRL required, for use as excipient
polysorbate 80	Table 1 of Annex to EU Regulation No 37/2010 no MRL required
simethicone emulsion 30%	out of scope list EMA/CVMP/519714/09 Rev 7
purified water (Aqua purificata)	out of scope list EMA/CVMP/519714/09 Rev 2

Withdrawal periods

Based on the provided residue depletion study performed at 24, 48, 72 and 96 hours with the final drug product formulation intended to be marketed, a withdrawal period of 4 days can be established for Panacur AquaSol when administered at the maximum recommended dose of 2.5 mg fenbendazole/kg bw/day for 2 consecutive days.

The withdrawal period is calculated using the alternative approach by taking the first time point where all concentrations are below the respective MRL (48 hours for muscle –when all the results were below the limit of quantification and 72 hours for liver, kidney and skin with fat – when all the results were below the limit of detection, except for two liver results that were below the MRL) and adding a safety span of 30%, resulting in a withdrawal period of 3 days for muscle, and 4 days for liver, kidney, and skin+fat. The overall withdrawal period for meat and offal for slaughter was established as 4 days.

Analytical methods

The HPLC method used in the residue depletion study has been validated in accordance with volume 8 of "The Rules governing medicinal products in the European Union". The method is suitable for the determination of the combined residues of fenbendazole, oxfendazole and oxfendazole sulfone as the sum of the extractable residues in swine tissues (muscle, Liver, kidney and fat + skin) which could be oxidised to oxfendazole sulfone in the range of 25-1000 µg/kg.

Overall conclusions on the residues documentation

The provided studies investigated the depletion of fenbendazole residues after administration of a fenbendazole suspension formulation to pigs or they describe the method analysing these fenbendazole residues. The studies are well described and performed.

Based on the provided residue depletion study a withdrawal period of 4 days could be established for Panacur AquaSol when administered at the maximum recommended dose of 2.5 mg fenbendazole/kg bw/day for 2 consecutive days.

Part 4 – Efficacy

Development of resistance

The development of nematode resistance to benzimidazoles has become a significant problem, but so far not in the pig, for which only sporadic reports on treatment failures exist, even after a 30-year use.

The risk for resistance development cannot be excluded, but will not be higher for Panacur AquaSol, compared to in-feed medication of fenbendazole. A suitable warning stating that frequent and repeated use of any anthelmintic could increase the risk for development of resistance is included in the SPC.

To reduce the risk of resistance development it is important that the water systems are always flushed or otherwise rinsed after medication to avoid that subtherapeutic concentrations of fenbendazole remain in the water systems.

Dose determination/justification

Two dose determination studies were carried out in animals after experimental infection with *Ascaris suum* embryonated eggs. The Panacur AquaSol treatment dose was 5 mg fenbendazole/kg bw as a single dose or as a split dose over 2 or 3 consecutive days and administered by drenching. Compared to untreated controls reductions were about 99% for larvae and over 94% for adult nematodes.

Four dose confirmation studies were carried out, 1 after natural infection and 3 after experimental infections. Infections concerned *Ascaris* and *Oesophagostomum*.

In the *Ascaris* studies, Panacur AquaSol was administered via the drinking water at a dose of 5 mg fenbendazole/kg bw for 1 day or as a split dose for 2 consecutive days.

In the *Ascaris* experimental infection studies, reductions in numbers of L_5 or adults was >93% after the single dose of 5 mg fenbendazole/kg bw and ~100% after the 2 days treatment (= 2x 2.5 mg fenbendazole/kg bw).

In an experimental infection with *Oesophagostomum*, the total dose of 5 mg fenbendazole/kg bw was divided over 2 consecutive days. Compared to an infected, but untreated control group, reduction was 100% on the basis of adult nematode counts.

It is anticipated that the dosing regimen for Panacur AquaSol (5 mg fenbendazole/kg bw divided over 2 consecutive days; i.e. 2.5 mg fenbendazole/kg bw/day) will exert similar efficacy, compared to efficacy levels reported in literature for conventional Panacur-formulations.

Field trials

A field study was carried out on 4 farms in the EU (France, Germany and Spain), including 432 animals, being naturally infected with predominantly *Ascaris suum*. A total of 332 animals were treated with Panacur AquaSol at the recommended dose rate of 5 mg fenbendazole/kg bw divided over 2 consecutive days; 100 animals were left untreated and kept as controls. Treatment efficacy was based on faecal egg output. Reductions in egg counts were 99.5-100%.

Another field study was carried out on 5 pig farms in Germany. A total 102 animals, infected with *Oesophagostomum* spp. were assigned to a treatment (58 animals) or control group (44 animals). Pigs excreting 200 eggs per gram of faeces were included. Panacur AquaSol was administered at the recommended dose rate of 5 mg fenbendazole/kg bw divided over two consecutive days. After Panacur AquaSol Treatment, no egg excretion was detected.

Overall conclusion on efficacy

It is concluded that the indications have been sufficiently substantiated.

Ascaris suum indication

Controlled clinical trials including a multicentric field study demonstrated that both migrating larval stages as well as (pre-)adult *Ascaris* were efficiently controlled after the proposed dosing of 5 mg fenbendazole/kg bw over 2 consecutive days (99-100% reduction).

Oesophagostomum spp. indication

Controlled clinical trials including a multicentric field study demonstrated that adult stages of *Oesophagostomum spp*. were efficiently controlled after the proposed dosing of 5 mg fenbendazole/kg bw over 2 consecutive days (100% reduction).

Hyostrongylus rubidus indication

A literature review on the efficacy of fenbendazole against *Hyostrongylus rubidus* was provided in support of the dosing regime of 5 mg fenbendazole/kg bw over 2 consecutive days. *Hyostrongylus rubidus* is a rare strongylid parasite in intensive herds and consequently was not detected in the field study or available for experimental infection. The applicant withdrew the indication for *Hyostrongylus rubidus* during the application procedure.

Ovicidal effect

Evidence for ovicidal activity of fenbendazole has been shown. Ovicidal activity, in addition to the elimination of the worm burden, helps to reduce environmental contamination with infective nematodes.

Part 5 – Benefit risk assessment

Introduction

Panacur AquaSol is a 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.

The active substance of Panacur AquaSol, fenbendazole, is a well-known benzimidazole anthelmintic which is already commonly used worldwide in deworming strategies of pigs and also in a variety of other animal species. It is proposed to be used for the treatment and control of gastro-intestinal nematodes in pigs. The innovative nature of Panacur AquaSol is that it is a new treatment formulation, produced as sub-micron size particles of the active fenbendazole. Panacur AquaSol is intended for the use in drinking water.

Benefit assessment

Direct therapeutic benefit

The direct benefit of the product relates to its value in the treatment and control of gastrointestinal nematode infections. Efficacy has been demonstrated against *Ascaris suum* (adult, intestinal and migrating larval stages), and *Oesophagostomum spp*. (adult stages). Furthermore fenbendazole is known to have an ovicidal effect on nematodes eggs.

Efficacy against *H rubidus* was however not proven.

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.

Risk assessment

Fenbendazole is well tolerated in pigs in clinical trials with the final formulation product irrespective of the sex, age and reproductive status of the animals. It has a well established use with extensive pharmacovigilance data available. During the clinical trials conducted the product was well tolerated with no adverse effects being observed.

Body weight of the animals needs to be checked to ensure administration of a correct dose. The water delivery system is flushed with medicated water to ensure accuracy of dosing.

Fenbendazole has been used safely in breeding sows and boars. Overdoses up to 10 times the recommended doses were well tolerated. Adverse effects have not been observed.

No contra-indications or special precautions for use in animals are considered necessary to be included in the SPC.

The risk for resistance development cannot be excluded, but will not be higher for Panacur AquaSol, compared to in-feed medication of fenbendazole. A suitable warning stating that frequent and repeated use of any anthelmintic could increase the risk for development of resistance is included in the SPC.

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).

The use of the product as recommended is not expected to pose an unacceptable risk to the environment.

Based on residue depletion data using the finished product a withdrawal period for meat and offal of four days was established.

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 pigs.

The formulation and manufacture of Panacur AquaSol is well described 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 has been set.

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

Conclusion

The available data adequately support the claimed indication. No unacceptable risks are identified. Consequently, the benefit risk balance is positive.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.