18 January 2018
EMA/73085/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for Panacur AquaSol (EMEA/V/C/002008/II/0015)

International non-proprietary name: fenbendazole

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 23 June 2017 an application for a type II variation for Panacur AquaSol.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

This variation is to add a new therapeutic indication (*Capillaria* spp. L5 and adult stages) in chickens and to modify the withdrawal period.

Current	**Proposed**
SPC section 4.2 Indications for use / Leaflet section 4. Indications Chickens: Treatment of gastro-intestinal nematodes in chickens infected with: - *Ascaridia galli* (L5 and adult stages) - *Heterakis gallinarum* (L5 and adult stages)	**SPC section 4.2 Indications for use / Leaflet section 4. Indications** Chickens: Treatment of gastro-intestinal nematodes in chickens infected with: - *Ascaridia galli* (L5 and adult stages) - *Heterakis gallinarum* (L5 and adult stages) - *Capillaria* spp. (L5 and adult stages)
SPC section 4.5 Special precautions for use / Leaflet section 12. Special warnings The efficacy of the veterinary medicinal product at the recommended dosage is not sufficient for the treatment of infestations with *Capillaria* spp. The absence of *Capillaria* spp infestation should be confirmed prior to use of the product. In case of *Capillaria* infestation another appropriate anthelmintic veterinary medicinal product should be used. Use of the product deviating from the instructions in the SPC may increase the risk of development of resistance.	**SPC section 4.5 Special precautions for use / Leaflet section 12. Special warnings** *[This whole paragraph will be deleted]*
SPC section 4.9 Amounts to be administered and administration route / Leaflet section 8. Dosage for each species Chickens: The dose is 1 mg fenbendazole per kg body weight per day (equivalent to 0.005 ml Panacur AquaSol).	**SPC section 4.9 Amounts to be administered and administration route / Leaflet section 8. Dosage for each species** Chickens: The dose is 1 mg fenbendazole per kg body weight per day (equivalent to 0.005 ml Panacur AquaSol) for the treatment of *Ascaridia galli* and *Heterakis gallinarum*. The dose is 2 mg fenbendazole per kg body weight per day (equivalent to 0.01 ml Panacur AquaSol) for the treatment of *Capillaria* spp.

<table>
<tr>
<td>The dose has to be administered on 5 consecutive days.

Dose calculation:
The required daily amount of product is calculated from the total estimated body weight (kg) of the entire group of chickens to be treated. Please use the following formula:

ml product/day = Total estimated body weight (kg) of chicken to be treated x 0.005 ml

<table>
<tr><th>Total body weight of chickens to be treated</th><th>Amount of product per day (ml/day)</th><th>Total amount of product (ml/for 5 days)</th></tr>
<tr><td>40,000 kg
160,000 kg</td><td>200 ml
800 ml</td><td>1,000 ml (5 x 200 ml)
4,000 ml (5 x 800 ml)</td></tr>
</table>

SPC section 4.10 Overdose symptoms
No adverse reactions have been observed at up to ten-fold overdose in pigs. No adverse reactions have been observed at up to 5-fold overdose in layers and broilers (aged 21 days). No adverse reactions have been observed at up to 3-fold overdose in breeders.

SPC section 4.11 Withdrawal periods / Leaflet section 10. Withdrawal periods

Chicken:
Meat and offal: 6 days
Eggs: zero days</td>
<td>The dose has to be administered on 5 consecutive days.

Dose calculation:
The required daily amount of product is calculated from the total estimated body weight (kg) of the entire group of chickens to be treated. Please use the following formula:

<u>Treatment of Ascaridia galli and Heterakis gallinarum:</u>
ml product/day = Total estimated body weight (kg) of chicken to be treated x 0.005 ml

<u>Treatment of Capillaria spp.</u>
<u>ml product/day = Total estimated body weight (kg) of chicken to be treated x 0.01 ml</u>

<table>
<tr><th>Total body weight of chickens to be treated</th><th>Amount of product per day for <u>1 mg FBZ/ kg</u> (ml/day)</th><th>Total amount of product (ml/for 5 days)</th><th><u>Amount of product per day for 2 mg FBZ/ kg (ml/day)</u></th><th><u>Total amount of product (ml/for 5 days)</u></th></tr>
<tr><td>40,000 kg
160,000 kg</td><td>200 ml
800 ml</td><td>1,000 ml (5x200 ml)
4,000 ml (5x 800 ml)</td><td><u>400 ml</u>
<u>1600 ml</u></td><td><u>2,000 ml (5x400 ml)</u>
<u>8,000 ml (5x1600 ml)</u></td></tr>
</table>

SPC section 4.10 Overdose symptoms
No adverse reactions have been observed at up to ten-fold overdose in pigs. No adverse reactions have been observed at up to <u>2.5</u>-fold <u>the maximum recommended dose of 2 mg fenbendazole/ kg body weight</u> in layers and broilers (aged 21 days). <u>In individual laying hens a transient effect on bone marrow and corresponding white blood cells was observed at 5-fold the maximum recommended dose of 2 mg fenbendazole/kg body weight administered for 21 days.</u> No adverse reactions have been observed at up to <u>1.5</u>-fold <u>the maximum recommended dose of 2 mg fenbendazole/ kg body weight</u> in breeders.

SPC section 4.11 Withdrawal periods / Leaflet section 10. Withdrawal periods

Chicken:
Meat and offal: <u>9</u> days
Eggs: zero days</td>
</tr>
</table>

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

Panacur AquaSol is currently indicated for use in chickens to treat infections with adult and pre-adult (L5) stages of *Ascaridia galli* and *Heterakis gallinarum*, at a dose of 1 mg fenbendazole per kg body weight (bw) for 5 consecutive days. With this variation, the label claim of Panacur AquaSol is to be extended to pre-adult (L5) and adult stages of *Capillaria* spp. For this indication, the daily dose is increased from 1 mg fenbendazole/kg bw to 2 mg fenbendazole/kg bw, while the treatment duration remains at 5 days.

The applicant has provided data illustrating the prevalence of helminth species in poultry. *Capillaria* spp. are prevalent in Europe and are reported to cause production losses.

2.1. Safety

2.1.1. User safety

In this variation, the proposed doubling of the dose means that the user will handle twice the volume of product. This is not considered to impact significantly the user risks previously identified. These risks have been addressed by the safety warnings in the SPC.

2.1.2. Environmental risk assessment

Panacur AquaSol has been authorised for use in chickens at a dose of 1 mg/kg bw per day, for 5 consecutive days. In this variation, a double dose (2 mg/kg bw per day for 5 consecutive days) is proposed for the treatment of *Capillaria* spp. Because of the increased dose, the risks for the environment have to be addressed.

An ERA was provided in accordance with the relevant VICH and CVMP Guidelines.

In Phase I, the calculated worst case PEC_{soil}'s ranged between 5.58 µg/kg for broiler breeders and 88.70 µg/kg for broilers. All values are below the trigger of 100 µg/kg, therefore the assessment can stop in Phase I, and a Phase II assessment is not necessary.

It can be concluded that the proposed dose increase does not cause unacceptable risks for the environment.

2.1.3. Residues and withdrawal period

Two studies investigated the residue depletion of fenbendazole and its metabolites in eggs (treatment period 5 and 7 consecutive days, respectively) and one study investigated the residue depletion of fenbendazole and its metabolites in edible chicken tissues (laying hens and broilers; treatment period 7 consecutive days) after administration of Panacur AquaSol. The design, conduct, and evaluation of the studies of the residue documentation were accurate and comply with current regulatory requirements. Hence, these studies are suitable for the determination of withdrawal periods for Panacur AquaSol in the chicken when administered at the recommended dose of 2 mg fenbendazole/kg bw/day for 5 consecutive days.

The highest residue levels were observed in liver and kidney. Moreover, higher residue levels were observed in broilers compared to layers. At day 5 after the last dose, the residues are below the MRLs in liver (500 µg/kg), muscle (50 µg/kg) and skin+fat (50 µg/kg) in both layers and broilers. At day 7 after the last dose, the residues are below the MRL in kidney (50 µg/kg) in both layers and broilers.

The maximum residue level in eggs was 707.19 µg/kg for the 5-days treatment study, measured at the last day of administration (laying day 4). For the 7-days treatment study, the maximum residue level in eggs was 878.99 µg/kg, measured at the last day of administration (laying day 6). All residue levels measured in eggs at all time points were therefore below the MRL of 1300 µg/kg.

The proposed withdrawal periods for the 2 mg dosing regimen were:

Meat and offal: 9 days
Eggs: zero days

It was noted that the samples in both egg studies were taken from the most prolific layers. The applicant explained that the egg laying activity does not influence the egg development process, i.e. the time period in which the drug can be deposited in the egg yolk and/or albumen. However, it was not made clear whether the drug levels per individual egg will be different with different laying activities when considering for instance that the amount of drug present in the animal's body may be distributed over more eggs, for hens with high laying activity, and therefore would result in lower plasma concentrations and subsequent in lower concentrations of drug per individual egg.

On the other hand, it was noted that the 0-day withdrawal period for eggs was established based on a residue depletion study where hens were administered a dose of 2 mg fenbendazole/kg bw for 7 consecutive days instead of the recommended 5 days, and therefore a 2 day longer treatment period. This gives an extra safety margin. It is also acknowledged that regulatory guidelines do not require the inclusion of laying hens at different egg production rates in residue studies, although test animals should be representative for the target animal population.

It was discussed whether a differentiated withdrawal period, based on dosage, could be accepted. For broilers, the withdrawal period matters and it would be unfortunate if treated broilers which have reached slaughter weight must be kept for a period which is not necessary in respect of ensuring consumer safety. Therefore, the currently established withdrawal period of 6 days for meat and offal when chickens are administered 1 mg fenbendazole/kg bw/day for 5 days is acceptable and can be maintained.

In conclusion, it is agreed on a differentiated withdrawal period, based on dosage, as follows:

Meat and offal: 6 days for 1 mg/kg bw dose
9 days for 2 mg/kg bw dose

The withdrawal period for eggs is zero days for both dosages.

These withdrawal periods are considered sufficient to ensure consumer safety, especially noticing that some of the residue depletion studies have been performed administering the product for 7 consecutive days, which is 2 days longer than the recommended dosing period.

2.2. Efficacy

2.2.1. Pharmacology

Pharmacology is considered to be sufficiently covered by the data in the original submission for application of the product in chickens, in combination with the information provided on the current situation with regard to chicken helminth resistance.

2.2.2. Target animal safety

The applicant provided five target animal safety studies (from which three studies were part of the original submission for the application in chickens) and a field study.

Two margin of safety studies at 1, 3 and 5 times the currently recommended dose of 1 mg fenbendazole/kg bw for 3 times the recommended treatment duration of 5 days performed in accordance with VICH GL43 requirements were part of the original submission for the application in chickens. These studies were previously assessed and the CVMP at the time considered the study results to sufficiently support safety in the target animal. At the time it was noted that in the margin of safety study in layers, the egg weight was significantly lower in the highest two treatment groups (3 and 5 mg fenbendazole/kg bw for 15 days), compared to the control group in the second half of the treatment period (1.2 gram).

A reproductive safety study at 3x the currently recommended dose of 1 mg fenbendazole/kg bw for a treatment duration of 21 days performed largely in accordance with VICH GL43 requirements was also part of the original submission. The study was previously assessed and the CVMP at the time considered the study results to sufficiently support reproductive safety in the target animal. It is noted that, in this study, a small but statistically significant lower number of eggs laid per hen was observed in the treated group (3 mg fenbendazole/kg bw for 21 days).

For the newly proposed indication – treatment of infections with *Capillaria* spp. L5 and adult stages – the recommended dose is 2 mg fenbendazole/kg bw (for 5 days). The applicant therefore performed two additional margin of safety studies at 10 mg fenbendazole/kg bw for 21 days, in broilers and in layers, respectively. Both studies were well designed and executed, in accordance with the principles outlined in VICH GL 43 and performed under GLP. In both studies, the treatment was generally well tolerated and no clinical or gross pathological abnormalities were observed that could be attributed to treatment. Differences in haematology and clinical chemistry parameters between treatment and control groups were, albeit statistically significant in some instances, small and transient. These differences are not considered to have clinical relevance. In the broiler study, decreased cellularity of the bone-marrow was observed in one of 32 necropsied treated birds and is considered likely an effect of treatment. In the study in layers, no significant effects of treatment on egg production or egg quality were observed. In the layers, decreased cellularity of the bone-marrow was observed in 4 out of 12 necropsied treated birds (3 birds necropsied on study day 22 and one bird necropsied prematurely on study day 14) and is considered likely an effect of treatment. In hens necropsied on study day 27 no abnormalities of the bone marrow were observed.

In light of the observed effect, the applicant has proposed the following wording in the SPC 4.10: "…A transient mild to moderate reduction in bone marrow cellularity accompanied by a transient reduction in peripheral white blood cell counts and heterophils was observed in 4 of 12 chickens administered an overdose of 10 mg fenbendazole/kg bodyweight for 21 consecutive days…" The

proposed sentence is considered acceptable.

A controlled GCP field efficacy and safety study with the newly proposed dose of 2 mg fenbendazole/kg bw was performed in layer and broiler breeder flocks. Treatment duration was 5 days (group 1) or 7 days (group 2). Mortalities during the treatment phase were in line with what was observed in the pre-treatment period, clinical abnormalities were not observed. For the layer flock in the treated group 1, a clear dip occurred in the laying rate at the time of treatment and the following week. Laying rate recovered to pre-treatment values between 2 and 4 weeks thereafter. It is noted that this dip did not occur in the layer flock at the same location that received a 7-day treatment, or in the breeder flocks. The applicant concluded that there were no significant effects on egg production or egg quality (hatchability). As mentioned above, further differences in laying rate and egg weight were observed in other studies. In the margin of safety study in layers provided in the original submission, there was a small (2%) but statistically significant reduction in egg weight in the highest treatment groups (3 and 5 mg fenbendazole/kg bw). In the original reproductive safety study, a statistically significant reduction in egg production (egg weight per week) was observed in the treated group (3 mg fenbendazole/kg bw for 21 days), which was likely due to a reduction in laying rate in the treated group. However, in the laboratory margin of safety study in layers there is no indication of a reduced laying rate in highly productive animals treated with a dose of 10 mg fenbendazole/kg bw. A slight and non-significant (2%) reduction in egg weight occurred, but this was restored to pre-treatment levels during the recovery phase. In conclusion, based on the available data it appears that the observed differences in egg laying rate in the field study and in some of the laboratory studies are not treatment related since there is no dose-effect relation. Effects on egg weight appear to have a dose relation but are small (2%) and appear to be transient. Therefore, the risk of the proposed treatment regimen to hens in lay (including breeders) is considered to be small.

Overall, it can be concluded that the treatment is well tolerated when performed in accordance with the SPC.

2.2.3. Dose finding studies

Two dose finding studies of appropriate design and of sufficient quality performed using birds with infections with *Capillaria* spp. were included in the original submission for application in chickens. It could be concluded that both treatment dose and treatment duration had an effect on efficacy and that *Capillaria* spp. were dose-limiting. The results indicate that the approved treatment of 1 mg/kg bw/day for 5 days is not effective against *Capillaria* spp., whereas the newly proposed dose of 2 mg/kg bw/day for 5 days was effective in both studies.

2.2.4. Dose confirmation studies

Four historical dose confirmation studies provided were appropriately designed and of sufficient quality. The first three studies were performed in Ireland, according to a very similar set up and using animals from the same source with similar *Capillaria* spp. infections (16 or 20 birds/group). In the first study, the currently proposed dose of 2 mg/kg bw/day for 5 days was effective against *Capillaria* spp. (93.3%), while in the second and third study efficacy percentages of only 66.6% and 68.9% were obtained. The low efficacy (66.6%) that occurred in the second study could be a consequence of underdosing; due to a suspected operator error, chickens were not treated with the intended dose of 2 mg/kg bw, but with 1.03 mg (-48.53%) to 1.46 (-26.79%) mg/kg bw/day. The

results of the study are therefore disregarded. The fourth study was performed in the USA and used 80 animals per group harbouring natural infections with *Capillaria obsignata*. The proposed dose was effective against *C. obsignata* in this study (92.1%).

Two additional dose confirmation studies were performed, at a dose of 2 mg fenbendazole/kg bw for 5 or 7 days. The studies were appropriately designed and of sufficient quality. In the first study, groups of 24 layers with natural infections were used, although the species level of *Capillaria* was not identified. Reduction of *Capillaria* spp. (pre-)adult worm burden was 89.8% for the 5 day duration, confirming the effectiveness of the proposed dosing regimen. When calculated separately, the efficacy of 90% was achieved for both adult and pre-adult (L5) worms. The second study was performed in groups of 88 broiler breeders with natural infections of *C. obsignata*. Reduction of *C. obsignata* worm burden was 99.5% after the 5 days treatment duration, confirming the effectiveness of the proposed treatment.

Because one dose confirmation study did not meet the VICH GL21 requirement of at least 90% efficacy, the applicant performed a pooled efficacy calculation of all 5 dose confirmation studies. The geometric mean worm count of all control animals was compared to the geometric mean worm count of all animals treated with 2 mg fenbendazole/kg bw/day for 5 days of the dose confirmation studies. The pooled analysis resulted in an efficacy of 90.6%.

Overall, the dose confirmation studies are considered to sufficiently support the claim for efficacy against *Capillaria* spp. (L5 and adult stages).

2.2.5. Field efficacy studies

One GCP field efficacy (and safety) study was performed at a dose of 2 mg fenbendazole/kg bw for 5 or 7 days. This study was well designed and of appropriate quality. The layer and broiler breeder flocks used in the study are considered representative for the field situation, with respect to breed, age and housing system, and a sufficient number of birds were included in the groups. Average pre-treatment infection levels for *C. obsignata* are considered adequate. Efficacy was calculated using geometric means, and exceeded the 90% level (99.6%).

Thus, the efficacy of the proposed treatment regimen as determined in the laboratory studies was confirmed under field circumstances.

3. Benefit-risk assessment of the proposed change

This product is authorised for the treatment of gastro-intestinal nematodes in chickens infected with *Ascaridia galli* (L5 and adult stages) and *Heterakis gallinarum* (L5 and adult stages). Fenbendazole is an anthelmintic belonging to the benzimidazole-carbamate group and it acts by interfering with the energy metabolism of the nematode. The product is administered in drinking water in dose of 1 mg fenbendazole per kg bw per day for 5 consecutive days. The product is an oral suspension containing 200 mg fenbendazole/ml. The withdrawal period is 6 days for meat and offal, and zero days for eggs.

The proposed variation is to add a new therapeutic indication (*Capillaria* spp. L5 and adult stages) in chickens. The dose for the proposed new indication is double the currently approved dose, and therefore a modification of the withdrawal period is proposed.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of Panacur Aquasol is its efficacy against *Capillaria* spp. infections in chickens, which was investigated in a large number of well-designed laboratory and field efficacy studies conducted to an acceptable standard. *Capillaria* spp. are reported to occur throughout Europe and may cause production losses and even clinical disease in some cases.

A well designed clinical trial conducted in accordance with GCP demonstrated that the product is efficacious against *Capillaria spp.* in both layers and broiler breeders.

Well-designed laboratory studies conducted to an appropriate standard provided sufficient support of efficacy against *Capillaria* spp. in chickens at the proposed dosing regimen. The efficacy was confirmed by the results of a well-designed and appropriately executed field study in layers and broilers.

Additional benefits

The additional indication increases the range of available treatment possibilities for *Capillaria* spp. and mixed helminth infections in chickens.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Administration of fenbendazole in accordance with SPC recommendations is generally well tolerated. After application of a 5-fold overdose for more than 3 times the maximum recommended treatment duration, the main reported adverse reaction was a transient mild to moderate reduction of bone marrow cellularity and associated transient reduction in peripheral white blood cell counts and heterophils.

Risk for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

Panacur Aquasol is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

Fenbendazole has been evaluated previously in respect to the safety of residues and MRLs have

been established for target species and food commodities concerned under this application (i.e. chicken meat/offal and eggs). Panacur AquaSol is not expected to pose a risk to the consumer of meat/offal and eggs derived from treated chickens when used according to the SPC recommendations.

3.3. Risk management or mitigation measures

Target animal safety:

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal.

User safety:

User safety risks have been identified; these risks have been addressed by the safety warnings in the SPC.

Environmental safety:

Fenbendazole is considered to be toxic to aquatic organisms. The veterinary medicinal product should not be allowed to enter surface waters. Appropriate warnings are included in the proposed SPC.

Consumer safety:

Sufficient withdrawal periods for meat/offal and eggs have been set.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, user safety and environmental safety. The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Panacur AquaSol can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication (*Capillaria* spp. L5 and adult stages) in chickens and to modify the withdrawal period.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA, IIIB and A