21 January 2013
EMA/808903/2012

Committee for Medicinal Products for Veterinary Use

EPAR type II variation for Panacur AquaSol

International non-proprietary name: Fenbendazole

Procedure No. EMEA/V/C/002008/II/0002

EU/2/11/135/001-003

Scope:

Type II variation No. C.I.6.a – Addition of a new therapeutic indication for treatment and control of gastro-intestinal nematodes in pigs infected with *Trichuris suis* (adult stages).

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

Table of contents

1. Background information on the variation

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 BV (the applicant), submitted to the European Medicines Agency (the Agency) on 8 June 2012 an application for a type II variation for Panacur AquaSol.

1.1.1. Scope of the variation

Addition of a new indication in pigs for treatment and control of gastrointestinal nematodes in pigs infected with *Trichuris suis* (adult stages).

Some linguistic changes to the Summary of product characteristics (SPC) and Package leaflet (PL) are also introduced to improve readability of the English text.

Current	Proposed
SPC **4.2 Indications for use, specifying the target species** Treatment and control of gastro-intestinal nematodes in pigs infected with: - *Ascaris suum* (adult, intestinal and migrating larval stages) - *Oesophagostomum spp* (adult stages) **4.9 Amounts to be administered and administration route (and leaflet section 8)** To ensure administration of a correct dose, … This procedure may need to be performed on both treatment days. The dose is 2.5 mg fenbendazole per kg body weight per day (equivalent to 0.0125 ml Panacur AquaSol). This dose has to be administered on 2 consecutive days. For each treatment day the medicated water needs to be prepared fresh. 3) Shake the suspension well before mixing. **7. Marketing Authorisation Holder** NL-5831 AA Boxmeer **9. Date of first authorisation** {DD/MM/YYYY} Immediate packaging **15. Marketing Authorisation Holder** NL-5831 AA Boxmeer **16. Marketing Authorisation Number**	**SPC** **4.2 Indications for use, specifying the target species** Treatment and control of gastro-intestinal nematodes in pigs infected with: - *Ascaris suum* (adult, intestinal and migrating larval stages) - *Oesophagostomum* spp. (adult stages) - ***Trichuris suis* (adult stages).** **4.9 Amounts to be administered and administration route (and leaflet section 8)** To ensure administration of the correct dose, … This procedure may need to be performed on all treatment days. The dose is 2.5 mg fenbendazole per kg body weight per day (equivalent to 0.0125 ml Panacur AquaSol). This dose has to be administered on 2 consecutive days. **For the treatment and control of *Trichuris suis* the dose has to be administered on 3 consecutive days.** For each treatment day the medicated water needs to be freshly prepared. 3) Shake the product well before mixing. **7. Marketing Authorisation Holder** NL-5831 **AN** Boxmeer **9. Date of first authorisation** **9 December 2011** Immediate packaging **15. Marketing Authorisation Holder** NL-5831 **AN** Boxmeer **16. Marketing Authorisation Number**

Current	Proposed
EU/0/00/000/000 EU/0/00/000/000 EU/0/00/000/000 **Package leaflet** **4. Indication(s)** For the treatment and control of gastro-intestinal nematodes in pigs infected with - *Ascaris suum* (adult, intestinal and migrating larval stages) - *Oesophagostomum spp* (adult stages)	**EU/2/11/135/001** **EU/2/11/135/002** **EU/2/11/135/003** **Package leaflet** **4. Indication(s)** For the treatment and control of gastro-intestinal nematodes in pigs infected with - *Ascaris suum* (adult, intestinal and migrating larval stages) - *Oesophagostomum* spp. (adult stages) - ***Trichuris suis* (adult stages).**

2. Scientific discussion

Panacur AquaSol is a fenbendazole-containing anthelmintic suspension for oral administration via the drinking water. It has been authorised for the treatment of pigs infected with adult and immature stages of gastrointestinal nematodes.

Fenbendazole (FBZ) 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. The safety of fenbendazole has been studied and described in detail (reference: EMEA/MRL/866/03-FINAL 2004).

The applicant submitted an application for variation to add the nematode species *Trichuris suis* (adult stages only) to the indication. *T. suis* can be found in caecum and colon. Infections may cause sufficient damage to allow secondary infections becoming established. Prepatency is about 45 days and worms can survive for up to 4–5 months. Larvae are lodged in the mucosa. From the adult worms anterior part is also lodged inside the mucosa. The posterior part emerges through the mucosal surface into the lumen.

Efficacy

Amounts to be administered and administration route remain the same. However, with respect to *T. suis* the applicant proposes to extend the treatment duration from 2 to 3 days.

In support of the new claim, the applicant submitted the results of 1 validation study, 2 dose determination studies, 4 dose confirmation studies and 1 field study for a fenbendazole (FBZ) suspension. Additionally the reports of 3 studies carried out with a FBZ premix have been included as well as 3 literature references on *Trichuris* infections.

Overview of results for the proposed indication are summarised in the table below.

Ref.	Study results
1.	1 mg/kg bw per day for 5 consecutive days resulted in high efficacy, with >99 % relative reduction of *T. suis* worm counts and egg output in **experimentally** infected pigs.
2.	No differences between 3 consecutive days and 5 consecutive days. Results indicate that for *T. suis* the minimum duration of treatment should be 3 consecutive days in **experimentally** infected pigs.
3.	A dose of 2.5 mg FBZ/kg administered 2 consecutive days was not sufficiently efficacious against adult stages of *T. suis* (including L5) in **experimentally** infected pigs.
4.	The optimal treatment period would be at least 3 consecutive days with a minimum of 2 mg FBZ/kg bw daily in **experimentally** infected pigs.
5.	A dose of 2.2 mg FBZ/kg bw administered through the drinking water for 3 consecutive days did reduce worm counts for *T. suis* >98 % when compared to untreated controls, in **experimentally** infected pigs.

6.	A daily dose of 2.5 mg/kg for 3 consecutive days reduced the number of *T. suis* worms by 73.6 % in **naturally** infected pigs
7.	A daily dose of 2.5 mg FBZ/kg over 3 consecutive days was significantly efficacious (93.5 % worm count reduction) in the treatment of pigs, **naturally** infected with *T. suis*.
8.	A daily dose of 2.5 mg FBZ/kg over 3 consecutive days reduced faecal egg output in pigs, **naturally** infected with *T. suis*. But reductions varied between farms, being 90 % when compared to untreated controls.

In complying with the recommendations made in VICH GL7 and maintaining the same daily dose as authorised, it is obvious that the duration of treatment should be extended. When administered for a 3-day period a dose of 2.5 mg FBZ/kg bw is sufficient to result in a >90 % reduction in worm counts when compared to untreated controls. However, as could be expected, reductions of >90 % are not always reproducible in naturally infected animals.

The CVMP considered that a 3-day treatment period is the shortest one possible when using a dose of 2.5 mg FBZ/kg bw. Considering results from studies with FBZ as a premix, an increase in treatment period can compensate for a lower dose.

The CVMP concluded that for the control of *T. suis* infection a daily dose of 2.5 mg FBZ/kg bw administered for 3 consecutive days is the minimum dosage to be effective, therefore preparation of panacur 20% suspension in drinking water should be carefully conducted.

Safety for the target animals

FBZ has a well-established use with recognised efficacy and an acceptable level of safety. For the original application the CVMP concluded that additional tolerance studies carried out with Panacur AquaSol would not produce any new information on the safety of FBZ. Information on overdoses is available and treatment periods being longer than currently proposed have been used without any adverse effects observed.

The extension of the treatment period from 2 to 3 days is therefore not considered to bring about any change in the safety of FBZ treatment.

No adverse events were observed in the submitted studies that could be related to FBZ-treatment.

Therefore the CVMP concluded that Panacur AquaSol is safe for the target animal when used as recommended for the treatment of pigs with *T. suis* infections.

Residue data

The authorised product for pigs has a posology of 2.5 mg/kg of body weight (bw)/day for 2 consecutive days administered via the drinking water. The authorised withdrawal period for this posology is 4 days for meat and offal.

The new proposed indication has the same dose but extended treatment duration of 3 consecutive days.

In addition to the clinical documentation submitted to substantiate the new claim, the applicant provided a justification for the withdrawal period in view of the new proposed posology. The applicant used the previously submitted and assessed residue data.

In the previously submitted study, 4 groups of 6 pigs (85–101 kg bodyweight) were given Panacur AquaSol at a dose of 2.5 mg/kg bw/day via drinking water on 3 consecutive days, which is the proposed dosing regimen to treat pigs with *T. suis* infections. This means that the new posology was already accepted in the previously submitted study on which the CVMP based the withdrawal period of 4 days.

In conclusion, the currently authorised withdrawal period of 4 days for meat and offal of pigs is valid for the proposed new posology.

Environmental risk assessment

In view of the new proposed posology with an extended duration of three days, the applicant provided an updated Environment risk assessment. The PEC-soil's for the new proposed posology were well below the trigger value of 100 µg/kg. It is concluded that a Phase II assessment is not necessary.

User safety assessment

The proposed longer treatment duration will not lead to any new risks than those already identified, and which are already appropriately mitigated by the recommendations for user safety in the current product literature.

3. Benefit-risk assessment

3.1. Benefit assessment

- Adequate efficacy against *T. suis* infection in pigs.
- The extension of the length of the treatment period from 2 to 3 days in case of *T. suis* infection, maintaining the authorised daily dose of 2.5 mg FBZ/kg bw.
- 2.5 mg FBZ/kg bw daily for 3 consecutive days is considered the minimum dosage.

3.2. Risk assessment

The risk of the product remains unchanged.

The issue of obtaining and maintaining the intended FBZ-concentration in the medicated drinking water has also been raised for the initial application of the product and was considered a minor issue.

3.3. Evaluation of the benefit-risk balance

It is expected that treatment against *T. suis* as recommended will reduce worm burden to clinically (and zootechnically) irrelevant levels. Complete elimination of nematodes is not necessary; infection should persist in order to induce immunity.

The benefit-risk balance remains unchanged.

No change to the impact on the environment is envisaged.

4. Conclusion

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

The CVMP also recomended that the product information on posology should be updated as follows:

The dose is 2.5 mg fenbendazole per kg bw per day (equivalent to 0.0125 ml Panacur AquaSol). For the treatment and control of *Ascaris suum* and *Oesophagostomum* spp. the dose has to be administered on 2 consecutive days. For the treatment and control of *Trichuris suis* the dose has to be administered on 3 consecutive days.

5. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annex I, IIIA and IIIB.