EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 June 2020
EMA/296009/2020
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Aivlosin (EMEA/V/C/000083/II/0078)

INN: tylvalosin

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

Rapporteur: Carina Bergman

Co-Rapporteur: Andrea Golombiewski

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact
Telephone +31 (0)88 781 6000
An agency of the European Union

Table of contents

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, ECO Animal Health Europe Limited (the applicant), submitted to the European Medicines Agency (the Agency) on 24 July 2019 an application for a type II variation for Aivlosin.

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

To include an additional indication for the granules for use in drinking water formulation: "treatment and metaphylaxis of swine respiratory disease associated with *Mycoplasma hyopneumoniae* and *Pasteurella multocida*". The applicant changed the proposed indication during the procedure to "treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs".
As consequence to the above change, amendments to the dosage and withdrawal period sections of the product information have been made.

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

The applicant received scientific advice from the CVMP on 12 April 2017. The scientific advice pertained to the clinical development of the dossier and has been followed by the applicant.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, ECO Animal Health Europe Limited (the applicant), submitted to the European Medicines Agency (the Agency) on 24 July 2019 an application for a type II variation for Aivlosin to include an additional indication for the granules for use in drinking water formulation: "treatment and metaphylaxis of swine respiratory disease associated with *Mycoplasma hyopneumoniae* and *Pasteurella multocida*". In response to questions, the applicant changed the proposed indication during the procedure to "treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs".

As consequence to the above change, amendments to the dosage and withdrawal period sections of the product information were proposed for this formulation.

It was noticed that the applicant also suggested a change for the dosing strategy for the treatment of *Lawsonia intracellularis* in order to harmonise the posology for the two indications (dosing based on the heaviest pig to be treated instead of average bodyweight). This was considered acceptable since implications of this suggested change regarding target animal safety and depletion of residues were covered by the proposed additional indication.

Part 3 – Safety

User safety

The safety of the user is determined by dermal effects of irritation and sensitisation, which represent qualitative risks without a threshold. The quantity of granules to which the user is exposed depends on the number of animals to be treated and not the dose. The current warnings and safety measures in the SPC are valid also for the new indication and the higher dose level.

Environmental risk assessment

The applicant provided an updated ERA including Phase I calculations (VICH GL6) on the new 10 mg/kg bw dose level and a Phase II assessment (VICH GL 38) using PEC values for the "worst case" scenario "weaners" as well as the results of environmental impact studies previously evaluated by CVMP, and estimation of risks for humans and groundwater ecosystems associated to tylvalosin in ground water (EMA/CVMP/ERA/103555/2015). Based on these data, the CVMP concluded that the dosing regimen of 10 mg tylvalosin/kg bw for 5 days does not represent any risk to the environment or to humans (via residues in ground water when used as drinking water). Tylvalosin is not considered as a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance.

Residues documentation

In the residue depletion study, the dosing strategy resulted in individual daily doses of 1.6 to 26.6 mg tylvalosin/kg bw. The study does therefore not fulfil the requirement laid out in VICH GL 48, which states that the highest intended treatment dose should be administered for the maximum intended duration, i.e. the resulting residue concentrations from individual animals treated at doses lower than 10 mg/kg bw are not valid to derive withdrawal periods suitable to ensure consumer safety for consumption of tissues derived from treated animals. To be able to set an adequate withdrawal period, it is critical that the minimum requirement of 4 animals dosed with the maximum intended dose at each time point is met. Based on a half-life of 2.2 hours for tylvalosin in plasma, and of approximately 12 hours or shorter for the

marker residues tylvalosin and 3-O-acetyltylosin (3-AT) in liver (a rough estimate based on that the liver residue levels decreased by 50% or more between 12 and 24 h following end of treatment), steady state in the liver is however assumed to have been reached at day 3 (i.e 4th dosing day) without any significant accumulation. Dose correction was therefore required for liver marker residue data from all pigs that received a lower dose than intended on days 3 and 4 by using the lowest dose received on these days.

As the stability of tylvalosin and 3-AT in liver samples stored at -20 °C was outside the acceptance criteria (± 15% change from baseline, see VICH GL 49) during the validation of the method, residues in liver tissues were corrected by using the differences from baseline of -36.4% for tylvalosin and of -43.6% for 3-AT at the MRL of 50 µg/kg, which represent the worst case, and are considered appropriate. For values < limit of quantification (LOQ) the correction factors were applied on measured figures. The corrected 3-AT concentrations which were below LOQ/2 (5 µg/kg) and had a potential to reach the MRL together with tylvalosin, were set to 5 µg/kg before calculation of the marker residue (sum of tylvalosin and 3-AT).

Due to the very different duration of quantifiable liver concentrations of tylvalosin and 3-AT (3-AT could only be quantified at 12 h whereas tylvalosin was quantified up to 96 h), together with the fact that depletion kinetics were not observed in the plot of the data (sum of tylvalosin and 3-AT), the available liver residue data are not considered valid for determination of a withdrawal period by the usual statistical method. The withdrawal period can therefore only be set by using the alternative approach and an appropriate safety span. Based on the recalculated liver residue data 24 h is the first time point after end of treatment when all liver marker residue concentrations (sum of tylvalosin and 3-AT) are below the MRL. Applying a 100% safety span, which is considered sufficiently large as both steps for corrections of underdosing and storage stability represent worst case corrections, results in a withdrawal period of 2 days.

Part 4 – Efficacy

Pharmacodynamics

Data describing the pharmacodynamic characteristics of the active substance in Aivlosin, tylvalosin has been submitted and assessed by the CVMP in conjunction with previous applications for market authorisation. The substance is a macrolide antibiotic with activity mainly against Gram-positive organisms and mycoplasma but also some Gram-negative organisms including *Lawsonia intracellularis*. Two time kill studies of *M. hyopneumoniae* against tylvalosin were presented in the current application that support previous conclusions that tylvalosin is bacteriostatic but could have bactericidal effects at higher concentrations. However, a bactericidal effect at the site of infection, as suggested by the applicant, could not be determined from the data presented.

The applicant presented data on the *in vitro* activity of tylvalosin against 40 strains of *M. hyopneumoniae* and 30 strains of *P. multocida* from European pigs with respiratory disease.

For *M. hyopneumoniae,* the MIC of tylvalosin was between 0.008 and 0.031 µg/ml, MIC_{50}=0.016 µg/ml, and MIC_{90}=0.031 µg/ml. From the limited data presented it appears that MIC for tylvalosin against *M. hyopneumoniae* is relatively stable across different areas in Europe and signs of increasing resistance have not been made evident.

For *P. multocida,* the MIC of tylvalosin for the limited number of strains tested was high (range 64 to >128 µg/ml, MIC50=128 µg/ml, MIC90>128 µg/ml). The applicant was of the opinion that *in vitro* MIC determination for tylvalosin is not useful to estimate clinical efficacy against *P. multocida* and that this assumption is supported by the results from the challenge studies claimed to provide support for

treatment efficacy against *P. multocida.* However, CVMP found that these studies were not sufficient to support the conclusion that there is no relationship between *in vitro* MIC and clinical *in vivo* efficacy for *P. multocida* and tylvalosin. The applicant was asked to provide additional pharmacodynamic data to support the claim for *P. multocida*. No additional data was submitted and consequently the question regarding a potential relationship between susceptibility data and clinical efficacy of Aivolsin for the treatment and methapylaxis of *P. multocida* in swine was not resolved. However, as an indication for *P. multocida* was subsequently withdrawn by the applicant, the issue was no further pursued.

Development of resistance

The applicant elaborated on the potential effect on development of resistance due to the extended use of the product from treatment and metaphylaxis of porcine proliferative enteropathy caused by *Lawsonia intracellularis* (approved 2009) to treatment and metaphylaxis of swine respiratory disease associated with *M. hyopneumoniae* and *P. multocida*. Aivlosin in form of premix and oral powder is authorised since 2004 for treatment and metaphylaxis of swine enzootic pneumonia caused by *M. hyopneumoniae* in pigs. The MAH concluded that no increase in MIC_{90} from 1997-2003 to 2011-2016 was indicated based on the recent tylvalosin susceptibility data reported from Spain (Tavio *et al*, 2014; MIC_{90}=0.06 µg/mL) and Hungary (Felde *et al*, 2018; MIC_{90} ≤0.25 µg/mL) and from Hungary, Belgium, UK, Spain (Pridmore, 2017, Study DWS/004/17: MIC range from 0.008 to 0.031 µg/mL).

The applicant focused the discussion on the potential risk for resistance development and transfer of public health concerns from food-born and zoonotic pathogens on *Campylobacter* spp, which was considered reasonable by CVMP although also other species like *Salmonella spp* and LA-MRSA may be of concern. Data collected since 2015 in the EU, based on literature, European wide, and national Member State surveys for the surveillance of *C. coli* was presented and summarised.

In humans, the proportion of *C. jejuni* isolates resistant to erythromycin was very low overall (2.1% from more than 22.000 strains) and higher in *C. coli* (11.0% from 2479 strains), with higher proportions of resistant strains in 5 out of 16 Member States (22.8 to 63.2% resistant strains). High-level erythromycin resistance (MIC>128µg/mL) was detected in about 15 % of *C. coli* from humans.

In pigs, data from Sweden, Finland, and the Netherlands reported during the last five to ten years demonstrated that susceptibility of *C. coli* to erythromycin was high (97.7-100%). Similarly, 46 *C. coli* strains isolated from pig meat in the Netherlands were all susceptible to erythromycin. For *Enterococci* isolated from faecal samples high resistance rate (39.5 % for *E. faecium* and 19.4 % in *E. faecium*) against erythromycin has been reported. According to the applicant's expert, these resistance levels have been stable or decreasing since 1998.

The high level of resistance for *C. coli* against macrolides reported in some studies and the new resistance mechanism mediated by the *erm(B)* gene is of some general concern as regards public health. Limited data is available to reflect changes in resistance levels over time. The impact of the *erm(B)* gene on public health risks related to the use of macrolides in animals has not yet been determined. The identification of transferable resistance implies higher probability of emergence and spread which needs to be monitored closely. The fact that macrolides can be of critical importance for the treatment of human infections emphazises the importance of further attention. Aivlosin premix has been used in pigs for more than 10 years for the treatment of *M. hyopneumoniae,* and it is not expected that the authorisation of Aivlosin granules for use in drinking water for the same indication would increase the use of the product. The shorter treatment duration and higher exposure to treated animals for the granules for use in drinking water as compared to the premix is beneficial from a resistance development perspective although the applicant's assumption that a bactericidal effect will be obtained is uncertain. CVMP

concluded that the risk for development of macrolide resistance of concern for the target animal and for public health is not considered to be increased, if Aivlosin granules for use in drinking water for pigs is introduced to the market.

Pharmacokinetics

A pharmacokinetic study was presented where tylvalosin and 3-*O*-acetyltylosin plasma concentrations were determined after repeated administrations of Aivlosin 42.5 mg/g premix (reference item) in feed or Aivlosin 625 mg/g granules (test item) in water to growing pigs.

Three groups of 10 pigs each were given Aivlosin as 42.5 mg/g premix (reference item) at the daily dose rate of 2.125 mg tylvalosin per kg body weight for 7 days, 625 mg/g granules (test item) at the daily dose rate of 2.125 mg tylvalosin per kg body weight for 7 days or 625 mg/g granules (test item) at the daily dose rate of 5 mg tylvalosin per kg body weight for 5 days. The study suggested that bioavailability is higher for the Aivlosin water soluble granules as compared to the premix mixed in feed. However, the fact that the animals were fasted for some hours before administration may have impacted on the absorption. This was considered to reduce the usefulness of the data to compare and conclude on plasma exposure of tylvalosin for the two different formulations during clinical use.

The data generated in this pharmacokinetics study was used for a PK/PD comparison to assess whether Aivlosin 625 mg/g granules for use in drinking water could be expected to provide comparable clinical efficacy as Aivlosin 42.5 mg/g premix. However, based on weaknesses in the conduct of the PK study and general limitations in the possibility to use PK/PD data to conclude on dosing appropriateness for macrolides, the PK/PD comparisons were not considered useful to conclude on an appropriate dosing strategy. Thus, CVMP concluded that justification of the proposed dosing strategy was dependent on the challenge studies and the clinical studies, as already outlined in the CVMP scientific advice.

Dose determination and confirmation

Dose determination was performed in two experimental challenge studies, one conducted in the USA using a *M. hyopneumoniae*-only challenge model, and another one in Europe using a dual challenge model with *M. hyopneumoniae* and *P. multocida*. The selected dose was confirmed in two studies using the same experimental models.

Dose determination

American study, M. hyopneumoniae:

The american study evaluated 3 doses of Aivlosin (5 mg, 7.5 mg, and 10 mg tyvalosin/kg bw) in a *M. hyopneumoniae* challenge model. Mixed sex pigs were randomly allocated into four groups, three treatment groups and one control (48 pigs in 8 pens per group). All animals were demonstrated to be naïve to *M. hyopneumoniae* and were of a susceptible age (5 weeks at arrival). Pigs were challenged at day 0 and day 1 with lung tissue homogenate containing a well characterised *M. hyopneumoniae* strain (10^4 ccu/ml) via the intra-tracheal route. Treatment was initiated on day 8. Lung lesion scoring at day 28 based on the percentage of the lung affected by lesions indicative of *M. hyopneumoniae* was used as the primary endpoint. Secondary endpoints included clinical (coughing score, respiratory score etc.) and bacteriological parameters (demonstration of *M. hyopneumoniae* in BALF by qPCR).

The least squares mean (LSM) of the pen mean lung lesion scores demonstrated no significant trend contrast between the groups (P=0.07) but descriptive data showed a numerical trend towards a reduction in lung lesion scores as the dose increased (lung lesion score: untreated, 27.8; 5 mg, 25.0; 7.5 mg, 23.7; and 10 mg, 23.1). Pairwise comparisons to the untreated control group were also non-significant

(P=0.28 for Aivlosin 5 mg/kg bw, P=0.12 for Aivlosin 7.5 mg/kg bw, and P=0.08 for Aivlosin 10 mg/kg bw). Due to the presence of *S. suis* in the herd, the MAH performed a *post hoc* analysis controlling for the presence of *S. suis*. These type of *post hoc* analyses are however regarded unacceptable and hence the results from this analysis are disregarded. Results from secondary clinical and bacteriological endpoints showed no significant trend contrasts in results from the four groups (0 mg, 5 mg, 7.5 mg, and 10 mg per kg bw). Thus, this study provided only weak support for the 10 mg tylvalosin/kg bw dosing regimen for treatment of *M. hyopneumoniae*.

European study, M. hyopneumoniae and P. multocida ("dual challenge"):
The European study evaluated 2 doses of tylvalosin (5 mg and 10 mg tyvalosin/kg bw) in a dual challenge model containing *M. hyopneumoniae* and *P. multocida*. The study included 52 mixed-sex, 5±1-week-old pigs confirmed to be free from antibodies against *M. hyopneumoniae*. The pigs were randomly allocated to six groups (8 pigs per group). Three groups were challenged with both ("dual challenge") *M. hyopneumoniae* (Days 0, 1 and 2) and *P. multocida* (Day 14); one group was challenged with *M. hyopneumoniae* only (Days 0, 1 and 2); one group with *P. multocida* only (day 14) and one group was left unchallenged. All challenges were by the intranasal route with recent strains. Treatment was initiated day 15. Lung lesion scoring at day 28 was used as a primary endpoint. Secondary endpoints included clinical (total clinical score day 16-28) and bacteriological parameters (load of *M. hyopneumoniae* in bronchoalveolar lavage fluid [cfu/ml in BALF] and recovery of *P. multocida* from lung tissue [cfu/g lung tissue]).

There were no significant differences in the primary efficacy endpoint lung lesion score between the treated and untreated pigs (P=0.13 and P=0.27, respectively, for the groups receiving 5 mg or 10 mg tylvalosin per kg bw) or between the two dose groups (P<0.05). The numerical differences were noted but considered limited (lung lesion score: 5 mg, 7.99; 10 mg, 9.64; untreated, 14.05).
M. hyopneumoniae counts from BALF (cfu/ml) were significantly lower in the 10 mg tylvalosin/kg bw group compared to the dual challenge control (P<0.01) and to the 5 mg tylvalosin/kg bw group (P<0.01). *P. multocida* counts from lung tissue were significantly lower in both treated groups (5 mg/kg group and 10 mg/kg group) as compared to the untreated control (P<0.01) but there were no significant differences between the two doses (P>0.05).

Pigs in both groups treated with Aivlosin granules for use in drinking water had lower clinical scores (P<0.01) compared with the dual challenged control.

Due to the lack of a significant outcome for the primary endpoint (lung lesions) and the questionable clinical relevance of the challenge model (see below) this study was not considered to provide robust support for the selected 10 mg/kg dose.

<u>Dose confirmation</u>

The selected dose of 10 mg tylvalosin/kg bw was investigated in two studies using the same experimental models as for dose determination, one conducted in the USA, and another one in Europe.

American study, M. hyopneumoniae:
The basic design of this study was similar to the American dose confirmation study detailed above. The study included two groups; one treatment group and one untreated control group (102 pigs in 17 pens per group). Challenge was performed as in the dose confirmation study but treatment was initiated at day 14 after infection (instead of day 8).

Two primary endpoints were used: pen mean lung lesion score at day 28 (scoring was performed as in the dose confirmation study) and frequency of swine respiratory disease (SRD) clinically affected cases. The applicant did not mention which should be used as the primary endpoint or whether the two

endpoints should be regarded co-primary.

The pen mean lung lesions scores were lower in the Aivlosin group (6.52) than in the control group (14.97, P<0.01). Only two SRD clinical cases were registered between day 15 and study end, both in the control group (P=0.48). Among the secondary parameters pen mean coughing score was significantly lower in pens receiving Aivlosin granules for use in drinking water (11.13) compared to unmedicated pens (23.46; P<0.01) and the mean log of *M. hyopneumoniae* genomic copies/mL detected by qPCR in BALF, was lower in the Aivlosin group (7.93) than in the control pigs (8.20, P<0.01).

In account of the significant outcome for the primary endpoint lung lesion score and relevant secondary endpoints this study was considered to bring support for the proposed dosing strategy 10 mg/kg body weight for 5 days. The lack of a significant result for the clinical primary endpoint (SRD cases) was regarded acceptable since infection with *M. hyopneumoniae* not always results in overt signs of clinical disease.

European study, M. hyopneomoniae and P. multocida ("dual challenge"):
The basic design of this study was similar to the European dose confirmation study. The study included two groups; one treatment group and one untreated control group (44 pigs in 11 pens per group). Challenge was performed as in the European dose confirmation study. Treatment with Aivlosin granules for use in drinking water was administered at 10 mg tylvalosin/kg bw from day 15 to day 20 to the 11 pens in the treatment group.

Two primary endpoints were used: pen mean lung lesion score at necropsy (day 27/28) and pen mean clinical score (comprising the sum of rectal temperature, demeanour, respiration, nasal discharge and coughing scores day 16 to day 22). The applicant did not mention which should be used as the primary endpoint or whether the two endpoints should be regarded co-primary.

There was a significant (P<0.01) reduction in pen mean lung lesions in Aivlosin treated animals (3.31) compared with untreated animals (8.37). The pen mean total clinical score was lower in the Aivlosin treated animals compared to the untreated controls, but the difference was not statistically significant (P=0.18). Among the secondary endpoints, the load of both *P. multocida* and *M. hyopneumoniae* in lung tissue and BALF, respectively was significantly lower in the Aivlosin treated group (P<0.01). Moreover, the number of lung lobes affected by consolidation was lower in the Aivlosin group (P=0.05) as well as the rectal temperature (39.24°C vs 39.36°C, P=0.03).

Due to weaknessness in the design of the dual challenge model (*M hyopneumoniae* and *P. multocida*, see discussion below), CVMP did not consider the study useful to support the proposed 10 mg/kg bw dose for a combined infection. It was noted however, that mean lung lesion scores as well as load of *M. hyopneumoniae* in lung tissue were significantly reduced, which was considered to provide some additional support for efficacy of the 10 mg/kg bw dose against *M. hyopneumoniae*. However, as an indication for *P. multocida* was subsequently withdrawn by the applicant, the issue was not further pursued.

Some concerns were initially raised regarding the design, conduct, and clinical relevance of the challenge models employed. For the *M. hyopneumoniae*-only challenge model, satisfactory responses were provided by the MAH, which allowed the CVMP to conclude that the model was generally suitable for its purpose. For the dual challenge model including *M. hyopneumoniae* and *P. multocida* it could not be determined that infection with *P. multocida* was fully established when treatment was initiated (24h post infection). Consequently, it could not be ruled out that the model overestimated the efficacy of Aivlosin against *P. multocida* since infections generally are easier to combat at an early stage. Moreover, it was considered that a suitable model for robust efficacy evaluation against mixed infections of *M. hyopneumoniae* and *P. multocida* should reproduce clear clinical signs of respiratory disease. The dual

challenge model employed only caused signs of overt clinical disease amongst a few animals. Due to these shortcommings, the CVMP did not consider the dual challenge model employed in the dose determination and dose confirmation studies to be suitable for evaluating efficacy of treatment against *P. multocida* in combination with *M. hyopneoumoniae*.

Taken together, the dose-determination studies provided no substantial support for the 10 mg/kg bw dose over the lower doses tested. However, the efficacy of the 10 mg/kg bw dose against *M. hyopneumoniae* was confirmed by the dose confirmation study from the USA with some support by the European dose confirmation study.

By contrast, neither the dose-determination, nor the dose-confirmation studies employing the dual-challenge model were considered to provide robust support for efficacy of any tested dose against *P. multocida* in combination with *M. hyopneumoniae.* However, as an indication for *P. multocida* was subsequently withdrawn by the applicant, the issue was not further pursued.

Target animal tolerance

To support target animal tolerance in the current application, the applicant referred to documentation submitted and assessed by the CVMP in conjunction with the application for Aivlosin 625 mg/g granules for use in drinking water for the treatment and metaphylaxis of ileitis in pigs caused by *Lawsonia intracellularis* (EMEA/V/C/083/X/032).

The proposed dose (10 mg/kg bw) is higher than the dose approved for the treatment and metaphylaxis of ileitis (5 mg/kg bw). It was noted that the doses tested in the previously performed target animal tolerance study fulfil the recommended dose multiples to be tested as outlined in the VICH guideline GL43 and cover also the current higher target dose of 10 mg/kg bw. There were 8 pigs (4M, 4F) in each dose group. In the tolerance phase Aivlosin was administered by gavage at 100 mg/kg bw (10 x recommended target dose, RTD) for 5 consecutive days. In the toxicity phase Aivlosin was administered for 15 days at 10 mg/kg bw (1x RTD, by gavage), 10 mg/kg bw (1x RTD, in drinking water), 30 mg/kg bw (3x RTD, by gavage), or 50 mg/kg bw (5x RTD, by gavage).

It was acknowledged that the challenge studies and the clinical studies presented by the applicant in support of the current application suggested that Aivlosin is well tolerated at a dose of 10 mg/kg (no AEs considered to be directly associated to Aivlosin treatment were reported in the challenge studies or in the field).

To ensure sufficient intake of active substance in all treated pigs the MAH proposed to base calculation of administered dose on the heaviest pigs in the group. The applicant proposed a corresponding change in section 4.9 also for the indication *Lawsonia intracellularis* (dosing based on the heaviest pig to be treated instead of average bodyweight). This approach was supported. There was some concern raised as to whether this may cause risk for overdose amongs small pigs when weight range is large within a group. It was however acknowledged that it is mainly the water intake rather than the body weight that determines drug exposure, and it was thus accepted that this dosing approach would likely not increase the risk for overdose. Nevertheless, to mitigate the risk of overdosing a statement that water consumption should be monitored was added to section 4.9 of the proposed SPC.

Clinical studies

The efficacy of Aivlosin granules for use in drinking water for the treatment and metaphylaxis of respiratory disease associated with *M. hyopneumoniae* and *P. multocida* was investigated in 5 field

studies conducted in Europe (Hungary, France, Spain (two studies) and Germany) with similar study design.

The purpose of this was to allow for pooling of data from the individual studies in a multicentric study. The pooling of data sets was regarded acceptable for studies with similar study protocol since this was pre-planned.

Support for the treatment claim was evaluated by non-inferiority trials against a positive control product, authorised for treatment of swine respiratory disease and containing either tylosin (200 mg/ml solution for injection, field studies in Hungary and France) or tiamulin (450 mg/g granules for use in drinking water, two field studies in Spain and one in Germany).

Support for the metaphylaxis claim was evaluated by superiority testing against untreated animals at 2 sites (field studies in Hungary and France), and by comparison to tiamulin at 3 sites (field studies in Spainand Germany).

The selected sites all had a history of respiratory disease, and presence of *M. hyopneumoniae* was indicated by results from lung inspections at abattoirs and confirmed by detection of the bacterium (isolation or by PCR) in samples from clinically affected animals prior to the study and in oral fluid samples collected at pen level at treatment inititation. *P. multocida* was detected in samples collected prior to treatment in three out of the five sites (sites with *P. multocida*: Studies from Hungary, France, and one from Spain). The suitability of the diagnostics used to confirm disease caused by *M. hyopneumoniae* and *P. multocida* is further commented on below (see the section "Diagnostic confirmation of *M. hyopneumoniae* and *P. multocida*").

Treatment and metaphylaxis started at day 0 when 1) pneumonia had been observed in necropsied pigs in the current group of pigs or in the abattoir in previous batches, if there were no mortalities associated to respiratory problems, 2) *M. hyopneumoniae* DNA had been detected in bronchoalveolar lavage fluid (BALF) from animals showing clinical signs of respiratory disease in the proposed study batch of animals, and 3) when 30% of the pens had at least 10% animals per pen classified as clinically affected.

A pig was declared clinically affected, if it had a respiratory score 1 (out of a range of 0 – 3) and a rectal temperature ≥40°C or a respiratory score >1 independently of rectal temperature. The same respiratory scoring system was used in all field studies (Nanjiani *et al*., 2005). Pigs clinically affected on day 0 were used for evaluation of treatment efficacy (treatment efficacy population) and pigs that were healthy on day 0 were used for evaluation of metaphylaxis (metaphylactic efficacy population).

Confirmation of *M. hyopneumoniae* and *P. multocida* in the herds

The CVMP raised concerns regarding the diagnostic confirmation of *M. hyopneumoniae* and *P. multocida* as the etiological cause of the respiratory disease treated in the field.

M. hyopneumoniae

The following information was made available to conclude on the potential relationship between *M. hyopneumonia* and signs of respiratory disease in the herds. At abattoir checks of preceeding batches of pigs (2-6 months prior to treatment initiation) typical lung lesions were present in 30-79% of examined lungs (48-141 lungs examined per site). At treatment initiation, clinical signs of respiratory disease were present in 29%-85% of the pens at the different sites. When treatment was initiated day 0, *M. hyopneumoniae* was detected in oral fluid samples by PCR in 5/21 (24%) pens at the site in Hungary, 0/36 (0%) pens at the site in France, 4/20 (20%) and 2/24 (8%) at the two sites in Spain, respectively, and in 4/24 (17%) pens at the site in Germany. From BALF samples collected from clinically affected pigs prior to treatment, *M. hyopneumoniae* could be demonstrated by PCR in 10/13 (77%) samples collected

at the site in Hungary, 4/15 (26.7%) at the site in France, 6/14 (43%) and 2/12 (17%) of the samples at the two sites in Spain, respectively, and in 3/12 (25%) samples at the site in Germany. Oral fluid samples were also collected at study end and demonstrated that *M. hyopneumoniae* still could be detected (all sites were positive at study end).

Taken together, this information was considered to provide adequate support for the presence of respiratory disease associated with *M. hyopneumoniae* at the selected sites. Key observations were the combination of typical lesions at abattoir checks, clinical signs of respiratory disease at treatment initiation, indication of on-going spreading of *M. hyopneumoniae* during the study period by PCR on oral fluid samples, and at four out of five sites confirmation of *M. hyopneumoniae* in BALF samples from clinically affected pigs around the time of treatment initiation.

P. multocida

P. multocida was isolated in 4 out of 13 pre-treatment BALF-samples collected at the site in Hungary, 8 out of 15 sampled pigs at the French site, and in 2 out of 14 samples at one Spanish site. Samples from the other two sites were negative. For the other Spanish site, the two samples collected from clinically affected pigs positive for *P. multocida* (and *M. hyopneumoniae*) were collected day -39 and can hence not be regarded representative for the disease present in the herd day 0.

Based on this, demonstration of *P. multocida* as a contributor to the respiratory disease observed and treated in the field studies was not considered to be confirmed. However, as an indication for *P. multocida* was subsequently withdrawn by the applicant, the issue was no further pursued.

Treatment claim

The primary endpoint for treatment efficacy was "treatment success" defined as the proportion of animals clinically affected at day 0 no longer clinically affected at treatment completion (day 5) and at the end of the study (day 13). The time point for primary efficacy assessment was not pre-determined but it was accepted that day 13 would be the most relevant time point. The clinical relevance of the criteria for defining "treatment success" was initially questioned since a pig with a respiratory score of 1 and body temperature of 40.0 C day 0 would be classified as a treatment success if the temperature dropped by 0.1°C at the end of treatment/study end. The applicant provided additional summary statistics demonstrating that only two pigs were classified as responders based only on a ≤0.5 °C drop in rectal temperature. Based on this, the primary endpoint was accepted for evaluation of treatment success against *M. hyopneumoniae*. For efficacy evaluation against *M. hyopneumoniae* in combinaton with *P. multocida* the endpoint was not considered suitable since treatment success was not consistently dependent on a change from feverish to non-feverish status.

Efficacy was evaluated with a non-inferiority test by comparison to the positive control at a non-inferiority margin set *a priori* at 20%. This analysis was performed individually for each of the five sites as well as on the pooled data sets Aivlosin vs tylosin and Aivlosin vs tiamulin. Results based on two-sided 95% CIs for the per protocol population are given below for the individual sites and the pooled data.

Individual sites

Aivlosin vs tylosin
Hungarian study:
Treatment success at study end (day 13) was 92% in the Aivlosin group (11/12) and 87% (13/15) in the tylosin group. The difference in treatment success was 5% (95% CI= -24%, 32%).

French study:
Treatment success at study end (day 13) was 72% in the Aivlosin group (13/18) and 25% (6/24) in the tylosin group. The difference in treatment success was 47% (95% CI= 17.5%, 77%). The results from this study were initially questioned since the control product failed to perform as expected. The MAH pointed out that the study was GCP compliant and that there was no indication of any systematic bias. Although these arguments were acknowledged the substantial deviation of the results of this study from the other four clinical studies was considered to bring some uncertainty as to the reliability of the outcome. For that reason, the results were accepted as supportive but not pivotal.

Aivlosin vs tiamulin

First Spanish study:
Treatment success at study end (day 13) was 68% in the Aivlosin group (23/34) and 76% (28/37) in the tiamulin group. The difference in treatment success was -8% (95% CI= -29%, 13%).

Second Spanish study:
Treatment success at end of treatment (day 13) was 96% in the Aivlosin group (25/26) and 100% (25/25) in the tiamulin group. The difference in treatment success was -4% (95% CI= -19%, 12%).

German study:
Treatment success at study end (day 13) was 58% in the aivlosin group (22/38) and 63% (22/35) in the tiamulin group. The difference in treatment success was -5% (95% CI= -27%, 17%).

Pooled data

Aivlosin vs tylosin:
Treatment success at study end (day 13) was 80% in the Aivlosin group (24/30) and 49% (19/39) in the tylosin group. The difference in treatment success was 31% (95% CI= 8%, 54%). Note that the results from the pooled tylosin data set only were considered supportive due to the uncertainties regarding the French site mentioned above.

Aivlosin vs tiamulin:
Treatment success at study end (day 13) was 71% in the Aivlosin group (70/98) and 77% (75/97) in the tiamulin group. The difference in treatment success was -6% (95% CI= -18%, 6%).

CVMP concluded that treatment efficacy of Aivlosin could be regarded supported by the pivotal pooled data from the tiamulin trials which demonstrated non-inferiority within the pre-set margin of 20% (difference in treatment success -6%; 95% CI= -18%, 6). CVMP felt that in account of the fact that this is an antimicrobial a somewhat lower non-inferiority margin may have been more relevant. However, the worst-case difference in treatment effect of -18% was regarded acceptable considering that treatment efficacy was supported also by other data. Additional support for treatment efficacy was considered to be gained from the tylosin trials (difference in treatment success was 31%; 95% CI= 8%, 54%). A clear positive outcome from the *M. hyopneumoniae* only challenge study and some additional support from the dual challenge study was also taken into account. It was also noted that Aivlosin premix is authorised for treatment and metaphylaxis against *M. hyopneumoniae* at a four times lower dose and that the PK data presented did not indicate that the bioavailability of the water-soluble granules was worse than for the premix.

By contrast, CVMP concluded that insufficient support had been presented for a treatment effect from the field studies regarding a combined infection with both *M. hyopneumoniae* and *P. multocida*, given

that the clinical symptoms noted were not typical for a combined infection and that the occurrence of *P. multocida* was not sufficiently demonstrated. In addition, support for efficacy against *P. multocida* was not obtained from the challenge studies. However, as an indication for *P. multocida* was subsequently withdrawn by the applicant, the issue was no further pursued.

Metaphylaxis claim

Metaphylaxis was evaluated as a primary efficacy endpoint at the two sites where the metaphylactic efficacy of Aivlosin was compared to a negative control (field studies in Hungary and France). Metaphylactic efficacy was evaluated as the frequency of new cases in pigs that were not clinically affected at day 0, and that were evaluated for 2 intervals: day 1-13 and day 5-13, using the same scoring system as presented for the assessment of treatment effect. The interval day 1-13 was considered the most relevant.

In the Hungarian study the frequency of new cases day 1-13 was 6% (15/239) in the Aivlosin group compared to 12% (27/219) in the negative control group (P=0.325). In the French study the frequency of new cases day 1-13 was 36% (59/165) in the Aivlosin group compared to 42% (66/157) in the negative control group day 1-13 (P=0.458).

The applicant also compared the metaphylactic effect of Aivlosin to that of tiamulin in three studies (the two Spanish studies and the German study). Since none of these studies included a negative control group (EMA/CVMP/627/2001-Rev.1), the results from these studies can only be regarded as supportive. The MAH provided post hoc analyses suggesting that the lower bounds of the 95% CIs for the difference in frequency of new cases between Aivlosin and tiamulin both for the period 1-13 and day 5-13 were above a NI-margin of -10%, which was however not pre-specified.

Taken together, it was noted that the two field studies including a negative control did not bring significant support for metaphylaxis. Furthermore, the other three studies did not include a negative control and non-inferiority calculations for the entire study period were performed post hoc. Based on this it was concluded that field data provided very limited support for metaphylaxis. However, in line with the current guideline (EMA/CVMP/627/2001-Rev.1) CVMP considered that efficacy for healthy but presumably infected in-contact animals can be deduced from a confirmed treatment effect on group level. Support for a metaphylactic effect of Aivlosin can hence be justified on basis of the demonstrated treatment effect.

3. Benefit-risk assessment of the proposed change

Aivlosin (active substance: tylvalosin) is an antimicrobial for use in pigs, chickens, pheasants and turkeys. The formulation "granules for use in drinking water for pigs" is already authorised for the treatment and metaphylaxis of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis,* at a dose of 5 mg/kg bw for 5 days, and with a withdrawal period (meat and offal) of 1 day.

Aivlosin is already authorised as oral powder and premix for medicated feeding stuff for pigs for the treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* at a dose of 2.125 mg tylvalosin per kg bodyweight per day in-feed for 7 consecutive days. This application was submitted to add a new indication to Aivlosin granules for use in drinking water for pigs: "Treatment and metaphylaxis of swine respiratory disease associated with *Mycoplasma hyopneumoniae* and *Pasteurella multocida*." In response to CVMP questions, this indication was modified during the procedure to "treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs".

The proposed dose for this new indication (10 mg/kg bw for 5 days) is higher than for the already authorised indication (PPE) for the same formulation and, consequently, a longer withdrawal period (2 days for meat and offal) was proposed for the new indication on basis of new data.

Since the proposed new indication is already authorised for another formulation, cross-reference was made to data relevant for the current application, that was previously submitted and assessed by the CVMP. In addition, scientific advice was provided on data bridging from the approved premix formulation to the granules for use in drinking water formulation by use of pharmacokinetic data. In its advice, the CVMP concluded that the bioequivalence concept could potentially have been useful to support efficacy, provided that the treatment period was equal, but since deviating treatment periods were proposed this was not considered an option. Furthermore, the use of PK/PD modelling to justify a new dosing regimen was questioned and CVMP advised that a new dose would need to be supported by new dose determination and dose confirmation studies as well as clinical field studies. The advice was followed by the applicant.

3.1. Benefit assessment

The proposed benefit of Aivlosin is its efficacy in the treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *M. hyopneumoniae*, which was investigated in four challenge studies (two dose determination studies and two dose confirmation studies) as well as in non-inferiority trials to tylosin and tiamulin in the field.

Treatment efficacy against *M. hyopneumonia* was demonstrated by a well-designed, GCP-compliant challenge study confirming efficacy of the selected 10 mg/kg bw dose in reducing lung lesions. In the field, treatment efficacy of Aivlosin against *M. hyopneumonia* was demonstrated to be non-inferior to tiamuline at a 20% non-inferiority margin by the combined results from three GCP trials. Non-inferiority to tylosin was also indicated from supportive field data consisting of combined results from two trials including tylosin as positive control. Metaphylactic efficacy against *M. hyopneumoniae* is considered to be justified by extrapolation from the demonstrated treatment efficacy on group level (EMA/CVMP/627/2001-Rev.1).

The claim against *P. multocida* was not considered to be sufficiently supported, and this claim was therefore deleted by the applicant during the procedure.

The benefits of the product concerning treatment and metaphylaxis of proliferative enteritis caused by *Lawsonia intracellularis* remain unaffected by this variation.

Additional benefits

The availability of Aivlosin as in-water formulation for treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *M. hyopneumoniae*, in addition to premix/oral prowder is considered a potential benefit, since severely diseased pigs tend to continue to drink even when their appetite is reduced.

3.2. Risk assessment

Risks for the target animal:

In target animal safety studies, tylvalosin was in general well tolerated in doses up to 10 times the RTD (by gavage). This was also supported by the clinical studies. The CVMP concluded that the risk for the target animal is acceptable when used according to the SPC.

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:

Aivlosin is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

Tylvalosin has been evaluated previously in respect to the safety of residues and MRLs have been established for pigs and food commodities concerned under this application. Aivlosin 625 mg/g granules for use in drinking water for pigs is not expected to pose a risk to the consumer of foodstuffs derived from treated animals when used according to the SPC recommendations. The withdrawal period established to ensure depletion of residues below the MRLs is 2 days.

Special risks:

No concerns have been identified relating to the potential for resistance emergence by the addition of the new indications.

3.3. Risk management or mitigation measures

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, environment and consumer and to provide advice on how to prevent or reduce these risks.

The withdrawal period is set at 2 days for meat and offal.

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.

Based on the data presented, the benefit-risk balance for including a claim for treatment and metaphylaxis of *M. hyopneumoniae* and *P. multocida* is deemed negative since the product has not been demonstrated to be efficacious against *P. multocida*.

The benefit-risk balance for including a claim for treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *M. hyopneumoniae* is deemed positive. The benefit of treatment and metaphylaxis of *M. hyopneumoniae* is supported by dose finding and field efficacy data and the product is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended.

Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded by majority that the application for variation to the terms of the marketing authorisation for Aivlosin can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

Inclusion of the additional indication "Treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs."

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:

A, I, and IIIB

As a consequence of this variation, sections 4.2, 4.4, 4.5, 4.9 and 5.1 of the SPC of Aivlosin granules for use in drinking water for pigs are are updated. The corresponding sections of the package leaflet are updated accordingly.

5. Divergent position on the CVMP opinion on a type II variation for Aivlosin (EMEA/V/C/0083/II/0078)

The undersigned wish to express a divergent position to the CVMP Opinion on this application for a Type II variation, for the reasons outlined below:

Tylvalosin is a well-known macrolide antimicrobial already authorised as Aivlosin premix for medicated feeding stuff for the treatment and metaphylaxis of swine enzootic pneumonia caused by *Mycoplasma hyopneumoniae*.

The variation application to add "Treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs" to the list of indications for Aivlosin 625 mg/g granules for use in drinking water for pigs is, however, not considered acceptable for the following reasons:

Inadequate dose determination

According to a previous CVMP scientific advice, data-bridging from the approved Aivlosin premix for medicated feeding stuff to Aivlosin granules for use in drinking water is hardly feasible as bioequivalence may be difficult to demonstrate due:
- to the high pharmacokinetic variability
- PK/PD modelling is not suitable to determine optimal treatment duration
- treatment with the Aivlosin granules for use in drinking water is intended for only 5 days compared to 7 days for the Aivlosin premix.

Hence, the intended dosing regimen should be justified by an adequate dose determination study and confirmed in a dose confirmation study as well as clinical field studies.

Neither of the two dose determination studies supported efficacy of any of the tested Aivlosin doses against *Mycoplasma hyopneumoniae*, nor demonstrated superiority of the 10 mg/kg bw dose over the lower doses tested. In the first dose determination study using a *Mycoplasma* only challenge model, neither the primary endpoint (lung lesion score), nor secondary end points differed between control animals and those treated with different doses of tylvalosin. The second dose determination study, using a dual challenge model with *Mycoplasma* and *Pasteurella*, also did not show an effect of tylvalosin treatment for one of the primary endpoints (lung lesion score) as well as most secondary endpoints.

Although lower clinical scores (second primary endpoint) in animals treated with tylvalosin were detected, it remains unclear, whether these may be attributed to efficacy against *Mycoplasma*, or *Pasteurella* or an immunmodulatory effect of tylvalosin, and thus cannot be used to support the proposed dose for a *Mycoplasma* only treatment claim.

While there was some evidence of a positive effect of tylvalosin against *Mycoplasma hyopneumoniae* in the two dose confirmation studies, the adequacy of the proposed dose of 10 mg/kg bw was not proven due to a lack of unambiguous study results. In the first dose confirmation study using a *Mycoplasma*-only challenge model, significant differences for the primary endpoint (lung lesion score) were found. However, scores for both control and treatment group were rather low compared to similar challenge studies. The clinical relevance of a score difference of 8.45 is questionable considering a scoring system allowing values between 0 and 100. Additionally, there was a lack of significant results for the second primary endpoint (number of swine respiratory disease cases), as well as some of the secondary outcome parameters. The second dose confirmation study using a dual challenge model with *Mycoplasma* and *Pasteurella* demonstrated that both, mean lung lesion scores as well as load of *Mycoplasma hyopneumoniae* in lung tissue can be reduced by Aivlosin treatment; however, flaws in the study design, low lung lesion scores in treated and control animals, a lack of significant results for the second primary endpoint (total clinical score), as well as some of the secondary outcome parameters lead to the conclusion that this study is not suitable to support the proposed 10 mg/kg bw dose for the treatment of *Mycoplasma hyopneumoniae* infections.

Overall, as preclinical data were insufficient, the adequacy of the proposed dose can solely be verified with field studies by demonstrating adequate treatment and metaphylactic efficacy.

Insufficient demonstration of treatment efficacy

Five field studies were conducted in different European countries, but none of those studies supported treatment efficacy of the proposed dose of 10 mg/kg bodyweight for five consecutive days.

One of those studies conducted in France could not be further considered as the constancy assumption was not met, and the positive control product failed to perform as expected. Furthermore, none of the other four field studies demonstrated non-inferiority of Aivlosin granules for use in drinking water in comparison to either tiamulin or tylosin, as the lower margin of inferiority varied between 19 and 29%, which is outside the acceptable non-inferiority (NI) margin of $\leq$15%. Albeit a pooling of data from the three tiamulin studies was feasible, however, a sufficient efficacy of Aivlosin could not be demonstrated for those pooled data either (lower NI-margin 18%). Even though the applicant was requested to substantiate as to why the used NI-margin of 20% was suitable, no sufficient explanations were given.

Furthermore, it should be noted that several other concerns pertaining the field studies could not be sufficiently addressed by the applicant, questioning the validity of the results from those studies.

The primary endpoint (fever + respiratory score) used to define animals with enzootic pneumonia and determine treatment success was not considered suitable for proof-of-efficacy against *Mycoplasma hyopneumoniae*. Considering that enzootic pneumonia is a multifactorial disease mostly caused by a co-infection with *Mycoplasma* and different other pathogens, and also single *Mycoplasma* infections are mostly associated with coughing without fever, then a treatment success based on reduced fever and respiratory scores cannot, with certainty, be related to efficacy against *Mycoplasma* but may also be attributed to successful co-treatment of other secondary pathogens (e.g. Staphylococci or Streptococci spp). This is supported by the diagnostics used, whereby there was no reduction of *Mycoplasma* after treatment.

Additionally, the causative role of *Mycoplasma* for the respiratory disease treated in the field studies is questionable. *Mycoplasma hyopneumoniae* was present on all sites, at the time of treatment initiation, as demonstrated by PCR. However, only 27/78 BALF samples (~35%) collected from clinically affected pigs prior to treatment, were positive for *Mycoplasma hyopneumoniae*. The presence of *Mycoplasma* in diseased animals was confirmed by PCR, only (except for 1 out of 68 pre-treatment samples with a positive culture result). However, the PCR methods used were not able to discriminate between colonised non-diseased animals and clinical diseased animals. Additionally, several other bacterial and viral pathogens associated with respiratory diseases were detected in those diseased animals that may also be causal.

Taken together, neither the field studies nor the challenge studies provided robust support for efficacy of Aivlosin at the proposed dose of 10 mg/kg bodyweight. Additionally, deleting the *Pasteurella* indication does not solve the issue that enzootic pneumonia is typically a polymicrobial infection, and with a high rate of secondary bacterial survivors from tylvalosin treatment, e.g., *Pasteurella* spp., then efficacy is low, at best.

The development of resistances might further be enhanced by the shorter treatment period of 5 days for Aivlosin 625 mg/g granules for use in drinking water instead of 7 days as approved for the Aivlosin premix.

Insufficient demonstration of metaphylactic efficacy

Three out of five field studies did not include a negative control group and thus metaphylactic efficacy could not be determined. Two field studies including a negative control did not bring any significant support for the metaphylaxis claim.

One of those negative controlled studies could not be further considered as the constancy assumption was not met and the positive control product failed to perform as expected. The results of the remaining (Hungarian) study did not support metaphylactic efficacy as well. On the one hand pre-planned study initiation criteria were not met and treatment was initiated too early, consequently infectious pressure was quite low leading to a low number of new cases by day 13 and a possible overestimation of metaphylactic efficacy. On the other hand, no superiority of the treatment with Aivlosin granules for use in drinking water could be shown in this study compared to untreated control animals between study day 1 and 13.

Taken together, it was concluded that field data provided no support for metaphylactic efficacy of Aivlosin 625 mg/g granules for use in drinking water against *Mycoplasma hyopneumonia* infections at the proposed dose of 10 mg/kg bw.

It is additionally noted that in line with the current CVMP guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) Aivlosin water soluble granules are intended to be mixed into drinking water, which allows only a claim for both treatment and metaphylaxis, as all animals will be treated independent of their individual clinical status. As sufficient treatment efficacy for Aivlosin water soluble granules on group level has not been demonstrated, metaphylactic efficacy cannot be claimed.

Benefit/Risk assessment

When used as recommended, the benefit of efficacy of Aivlosin granules for use in drinking water for the treatment and metaphylaxis of swine enzootic pneumonia caused by susceptible strain of *Mycoplasma hyopneumoniae* at the proposed dose of 10 mg/kg bw is not supported by dose finding and field efficacy data.

In addition, with a high rate of secondary bacterial survivors, and tylvalosin exposure to the gastrointestinal tract microflora (for the metaphylaxis cases) as well as a shorter treatment duration compared to Aivlosin premix, a broad usage of Aivlosin granules for use in drinking water for the treatment of *Mycoplasma hyopneumoniae* associated pneumonia, however, provides optimal conditions for the selection and proliferation of antimicrobial resistance.

In the view of the undersigned, the overall benefit-risk balance for the proposed variation is negative.

Amsterdam, 20 May 2020

Esther Werner

Katarina Štraus

Niels Christian Kyvsgaard

Petra Falb

Leona Nepejchalová

Judita Hederová

Cristina Muñoz Madero

Bruno Urbain

Keith Baptiste

Hanne Bergendahl

Ricardo Carapeto García