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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Draxxin (EMEA/V/C/000077/II/0031)

International non-proprietary name: Tulathromycin

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

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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, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for DRAXXIN.

1.1.1. Scope of the variation

Type II variation No C.I.6.a is to add a new therapeutic indication, i.e. the addition of a new pathogen in swine respiratory disease (SRD), *Bordetella bronchiseptica*.

Current	**Proposed**
SPC **Section 4.2 Indications for use, specifying the target species** Pigs Treatment and prevention of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae and Haemophilus parasuis* sensitive to tulathromycin. ……....	SPC **Section 4.2 Indications for use, specifying the target species** Pigs Treatment and ~~prevention~~ metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae, ~~and~~ Haemophilus parasuis and Bordetella bronchiseptica* sensitive to tulathromycin. ……...
Package leaflet **Section 4. Indication(s)** Pigs See above.	Package leaflet **Section 4. Indication(s)** Pigs See above

Scientific discussion

Draxxin is authorised in the EU in pigs for the treatment and prevention of swine respiratory disease (SRD) associated with *A. pleuropneumoniae, P. multocida, M. hyopneumoniae* and *H. parasuis,* sensitive to tulathromycin. This variation is to add a new pathogen, *B. bronchiseptica,* to the existing indication; also the indication is amended in line with current guidance (the term "prevention" is replaced by "metaphylaxis"). The dosage regimen and withdrawal period for the new indication is the same as the approved.

2. Safety assessment

Cross-reference is made to safety and residue data previously submitted and assessed. New data submitted with this variation are outlined below.

2.1. Environmental risk assessment

An environmental risk assessment (ERA) was provided in accordance with VICH GL 6- Ecotoxicity Phase 1 (CVMP/VICH/592/98-Final) and EMA guideline in support of VICH guidelines 6 and 38 (EMA/CVMP/ERA/18282/2005-Rev 1). The PEC_{soil} values for intensively reared pigs dosed once with 2.5mg/kg bw are well below the 100 µg/kg threshold. Therefore, no further assessment is required and the potential environmental exposure to tulathromycin following recommended use is considered negligible.

2.2. Development of resistance

A microbiology safety expert report dated 2014 was provided, based on 161 related study reports and publications dated mainly from the last 15 years and in most parts identical to that provided for a previous procedure (EMEA/V/C/000077/X/0026). It had been updated with recent data published by EFSA, ECDC and supplemented by MIC data for the claimed target pathogen *B. bronchiseptica*.

Zoonotic and human commensals

The most important zoonotic and commensals pathogens regarding human health were studied, including *Campylobacter, Enterococcus, Salmonella,* and *Staphylococcus aureus*. The report followed the requirements of VICH-Guideline 27 on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL), concluding that no potential public concerns are expected to rise as a result of the addition of *Bordetella bronchiseptica* for the treatment and metaphylaxis of swine respiratory disease (SRD) under the proposed conditions of use.

Target pathogen(s)

The assessment has been updated and supplemented by specific data for the relevant indication in this application (*B. bronchiseptica*). MICs of tulathromycin determined for recent European strains of the target pathogen had MIC_{50} and MIC_{90} of 8 µg/ml, and a monomodal susceptibility distribution profile. No resistant isolates of *B. bronchiseptica* were found. The evolution of the susceptibility profile of already authorised target pathogens revealed no shift in susceptibility amongst these organisms since the launch of DRAXXIN in 2003.

Conclusions:

Overall, no animal or public health concerns in regard to development of resistance are expected by the addition of SRD associated with *Bordetella bronchiseptica* as a new indications for DRAXXIN.

3. Efficacy assessment

Cross-reference is made to pre-clinical data (pharmacodynamics, target animal tolerance) previously submitted and assessed. New data in regard to pharmacodynamics and new clinical data have been submitted, as outlined below.

3.1. Pharmacodynamics

The MICs and MBCs of a total of 159 *B. bronchiseptica* strains against tulathromycin were determined in a well-conducted GLP compliant study from 2014 (A621Z-GB-13-083), by broth microdilution according to approved standard according to CLSI. Of these strains, 115 strains were derived from the CEESA's Vetpath III program and 44 strains from the applicant's European field studies (A121C-DE-13-072 and A121C-ES-13-085). All strains were isolated between 2008 and 2012 from pigs with respiratory disease in Belgium, Denmark, France, Germany, Poland, Spain, the Netherlands and the United Kingdom. The strains derived from the CEESA program were epidemiologically unrelated, while for the strains isolated within the field studies an epidemiological relation had to be assumed. If these strains were excluded from the total MIC results, the MIC_{50} and MIC_{90} values remained unchanged, which confirmed that MIC results of potentially related field strains did not bias the results.

The susceptibility profile determined for 159 *B. bronchiseptica* isolates and tulathromycin was found to be monomodal, ranging from 2 to 32 µg/ml with a MIC_{50} and MIC_{90} of 8 µg/ml. Taking into account the clinical breakpoints established by CLSI for tulathromycin in SRD and *B. bronchiseptica* (S: ≤16 µg/ml, I: 32 µg/ml, R: ≥64 µg/ml), these strains are considered as susceptible, with only one isolate found to be intermediate susceptible. The $MBC_{50/90}$ determined in this study was likewise found at 8 µg/ml.

Time-kill kinetics of tulathromycin were investigated in a non-GLP compliant study in 2014 (A671Z-US-14-035). Three *B. bronchiseptica* strains with a MIC of 8 µg/ml were tested at 1X, 4X, 8X, and 16X the MIC at 3, 6, and 24 hours post-inoculation. The study confirmed the time dependent and bacteriostatic activity of tulathromycin. However, no conclusions regarding the bactericidal activity could be draw as only three strains were studied, and results were variable at 1X, 4X and 8XMIC, depending on the strain.

3.2. Dose justification

The applicant justified the proposed dose based on the currently authorised dose of 2.5 mg tulathromycin /kg bw (DRAXXIN 25 mg/ml) for the treatment and prevention of SRD associated with other pathogens, i.e. *A. pleuropneumoniae, P. multocida, M. hyopneumoniae* and *H. parasuis*. In addition, the same dose is already authorised in the U.S. for the "treatment of SRD associated with *B. bronchiseptica*".

Taking into account the MIC data of all the target pathogens, CVMP considered that *B. bronchiseptica* is not a dose limiting target pathogen, and in principle accepted the justification. Due to the high risk of infection for animals in contact with those showing clinical signs, the Committee also considered that a metaphylactic treatment would be fully recommended. Provided that efficacy of DRAXXIN in the therapeutic treatment of SRD associated with *B. bronchiseptica* is demonstrated, the CVMP agreed that a claim for "metaphylactic treatment" would be considered acceptable. However, the indications (for all the target pathogens) should be amended accordingly, i.e. the term "prevention" should be replaced by "metaphylaxis" in line with the Q&A document for the CVMP guideline for the SPC of antimicrobials (EMA/CVMP/414812/2011-Rev.1, October 2014).

The results of the clinical trials carried out to demonstrate the efficacy of DRAXXIN for the treatment and metaphylaxis of SRD associated with *B. bronchiseptica* confirmed the efficacy of the proposed dose.

3.3. Treatment of SRD associated with Bordetella bronchiseptica

Two new GCP compliant controlled, randomized and blinded clinical field studies were conducted, one in Germany (A121C-DE-13-072) and one in Spain (A121C-ES-13-085), to evaluate the efficacy of DRAXXIN 25 mg/ml in the therapeutic treatment of naturally occurring Swine Respiratory Disease (SRD) associated with *Bordetella bronchiseptica*. In both studies, another macrolide (tildipirosin) was used as positive control, for comparison and non-inferiority testing.

3.3.1. German field study (A121C-DE-13-072)

The study was conducted in Germany in 2013 at a single location, a pig farm with known history of SRD associated with *B. bronchiseptica,* and included 186 pigs aged 6 weeks suffering from pyrexia and moderate or severe clinical signs of SRD (depression, dyspnoe, coughing, sneezing). The presence of the target pathogen, *B. bronchiseptica,* but also other pathogens, in particular *H. parasuis* and *S. suis*, was confirmed by broncho-alveolar lavage (BAL) prior to treatment. Groups of pigs were treated once intramuscularly on day 0 with either tulathromycin 2.5 mg/kg bw (DRAXXIN 25 mg/ml) or tildipirosin 4 mg/kg bw. The animals were clinically observed and rated at regular intervals until day 21 using a combined score (clinical signs of SRD absent (0), mild (1), moderate (2) or severe (3)), and rectal temperature measurements were performed. The primary efficacy endpoint was the clinical cure rate (SRD score ≤ 1) on day 14. Non-inferiority to the comparator product was calculated based on the clinical cure rate on day 14, applying a non-inferiority margin of 15%.

Tulathromycin was shown to be non-inferior to the comparator product (tildipirosin) based on a clinical cure rate of 93.7% (tulathromycin) and 93.4% (tildipirosin) on day 14. The lower limit of 95% CI was -0.069 and thus greater than -0.15. Relapse rates (secondary endpoints) of 2.4% and 4.5% on day 21 were not significantly different between the treatment groups.

As pigs in both treatment and control group showed persistent severe pyrexia (mean rectal temperature above 40°C) and reduced feed intake on day 2, sodium salicylate was administered to the groups for three days to reduce pyrexia. Furthermore, at day 11 diarrhoea associated with haemolytic *E. coli* was confirmed in some animals, and additional antimicrobial treatment was initiated (colistin in feed). Some pigs received parenteral antimicrobial therapy and were withdrawn from the study. Infection with Swine Influenza Virus (SIV) was confirmed. This co-infection usually leads to increased *B. bronchiseptica* colonisation in the lower respiratory tract of pigs enhancing production of inflammatory mediators with exacerbated pulmonary lesions. Thus, the relevance of *B. bronchiseptica* in the incidence of sickness was accepted.

The effect of the concomitant treatments is not expected to have considerable impact on the assessment of efficacy; colistin does not act systemically so improvement of respiratory clinical signs due to the treatment of diarrhoea is not expected. Also, colistin and sodium salicylate treatments might have had an effect on the overall wellbeing of the animals but an impact on the assessment of the efficacy of DRAXXIN due to the administration of such concomitant treatments is not expected as the endpoint differentiating success/failure treatment in the SRD score were based on respiratory clinical signs, not affected by the concomitant treatments administered.

The choice of the primary efficacy parameter and the SRD scoring system combining different clinical signs (depression, dyspnoe, coughing, sneezing) not including more objective parameters e.g. rectal temperature, although not fully objective, is deemed as the most appropiate choice for this respiratory disease where it is known that *B. bronchiseptica* does not necessarily induce pyrexia (Rutter et al.(1982), Brockmeier et al. (2002)

3.3.2. Spanish field study (A121C-ES-13-085)

A second study was conducted in 2014 in Spain at a single location, a pig farm with known history of SRD associated with *B. bronchiseptica, which* included 192 pigs aged 4-5 weeks suffering from moderate or severe clinical signs of SRD (depression, dyspnoe, coughing, sneezing). The presence of the target pathogen *B. bronchiseptica,* but also other pathogens, in particular *H. parasuis* and *P. multocida* were confirmed by trachea-bronchial lavage prior to treatment. Groups of pigs were treated once intramuscularly on day 0 either with tulathromycin 2.5 mg/kg bw (DRAXXIN 25 mg/ml) or tildipirosin 4 mg/kg bw. The animals were clinically observed and rated using a combined score (clinical signs of SRD absent (0), mild (1), moderate (2) or severe (3)) at regular intervals until day 21. Rectal temperature measurements were performed. The primary efficacy variable was the clinical cure rate (SRD score ≤ 1) on day 14 with the objective to demonstrate non-inferiority (non-inferiority margin 15%) of tulathromycin compared to tildipirosin. Secondary variables were SRD related mortality, prevalence and severity of clinical signs, relapses on day 21, rectal temperature, and average daily weight gain.

Tulathromycin was shown to be non-inferior to tildipirosin based on percentage of clinical cure on day 14 with 100% clinical cure in the tildipirosin-treated group vs 98.9% in the tulathromycin-treated group. There were no significant differences between treatment groups regarding rectal temperature and day 21 relapse rate (secondary endpoints). Until study day 14 diarrhoea of unidentified origin was observed in a great proportion of pigs of both treatment groups, all pigs therefore received additional oral treatment with colistin and zinc-oxide. This medication was already used as pre-treatment before study initiation.

The CVMP agreed that clinical signs as well as the results of bacteriological examinations indicate efficacy of DRAXXIN in the treatment of SRD associated with the target pathogen *B. bronchiseptica* and other facultative pathogenic germs (in particular *H. parasuis* and *P. multocida* which were also identified in a (great) number of samples, where the role of B. bronchiseptica as the primary pathogen seems clear.

Omission of rectal temperature as inclusion criterion, as criterion for post-inclusion withdrawal and as part of the primary efficacy parameter is deemed acceptable as it is known that *B. bronchiseptica* does not necessarily induce pyrexia (Rutter et al. (1982), Brockmeier et al. (2002)).

In addition, diarrhoea of unidentified origin was observed up to day 14 in a great proportion of pigs of both treatment groups, and treated with additional medications. Evaluation and assessment of the antimicrobial treatment effect on SRD is not expected to be impacted by concomitant treatments (the comments relating to the effect of concomitant treatments made to the first field study in Germany (see above) also apply here).

Conclusions on the field studies

In summary, the CVMP considered that both studies could be accepted. The CVMP acknowledged that statistically both studies showed non-inferiority of DRAXXIN as compared to tildipirosin and that the major shortcomings had been resolved to demonstrate efficacy of DRAXXIN in the proposed new indication, in particular for the following reasons.

A proper diagnosis of SRD associated with *B. bronchiseptica* under the study conditions has been established. Based on published literature, the clinical signs observed and the pathogens isolated in both studies, the role of *B bronchiseptica* as the primary pathogen was accepted.

The combined scoring system as primary efficacy variable is deemed suitable taking into account that i) it includes typical clinical signs of SRD, ii) Intra-assessor reliability of the scoring is confirmed as the relevant assessments on Day 0, Day 14 and Day 21 were performed by one and the same assessor in each of the two countries. Taking into account that the endpoint applied in the scoring is based on the objective clinical signs sneezing and coughing, any potential inconsistencies would not have impact on the assessment of success/failure of the treatment, and iii) -as mentioned previously the endpoint differentiating success and

failure of the treatment is based on two typical respiratory clinical signs associated to *B. bronchiseptica*: coughing and sneezing, avoiding the inclusion of the most subjective clinical observations as part of the endpoint. The impact of concomitant diseases (viral co-infection/ diarrhea) requiring additional treatments on the clinical signs of SRD and efficacy assessment of the test/ reference product can be excluded. Colistin is not absorbed in the gastrointestinal tract and does not act systemically, so it is not expected to have effect on the respiratory clinical signs. Although concomitant treatments might have had an effect on the overall wellbeing of the animals, clinical signs related to the respiratory disease (which predominantly determined the overall SRD score) would not be affected.

3.4. Prevention / metaphylaxis of SRD associated with B. bronchiseptica

No clinical studies were submitted in support of the prevention (now metaphylaxis) of SRD associated with *B. bronchiseptica.* Instead the applicant provided a justification for the omission of such studies, based on the rationale laid down in the current draft revised guideline (EMA/CVMP/261/180/2012); i.e. that a metaphylactic claim could be accepted for certain pathogens, if therapeutic efficacy has been confirmed by clinical studies.

Given that *B. bronchiseptica* in SRD is almost considered a facultative pathogen and rapidly spreading in a clinically affected herd via aerosol with an incubation phase of 4-5 days, the CVMP considered this approach in principle as acceptable.

Studies provided support the efficacy of DRAXXIN in the treatment of SRD associated with *B. bronchiseptica*. Nevertheless it is proposed to amend the wording in section "Indication for use", of the product literature and replace "Treatment and prevention of …" by "Treatment and metaphylaxis of ….." in line with the Q&A document for the CVMP guideline for the SPC of antimicrobials (EMA/CVMP/414812/2011-Rev.1).

4. Benefit-risk assessment

4.1. Benefit assessment

The direct benefit of the product is the therapeutic and metaphylactic treatment of swine respiratory disease (SRD) associated with *Bordetella (B.) bronchiseptica* sensitive to tulathromycin.

Pharmacodynamic data confirmed the time dependent and bacteriostatic activity of tulathromycin against *B. bronchiseptica*, and *in-vitro* susceptibility was demonstrated by a well-conducted European study (2008-12) using strains isolated from pigs with respiratory disease. Based on the MIC data, the CVMP in principle accepted the applicant's dose justification that *B. bronchiseptica* is not the dose limiting target pathogen, and to apply the existing dosing scheme also for this pathogen, provided that clinical data would support the efficacy adequately.

In support of the clinical efficacy of *DRAXXIN* (single i.m. dose of 2.5 mg/kg bw) in the treatment of naturally occurring SRD associated with *B. bronchiseptica*, two European field studies were conducted, using another macrolide (tildipirosin) as positive control. In both studies, DRAXXIN was non-inferior to tildipirosin based on the assessment of clinical cure rate and relapse rates.

Both studies showed major shortcomings that were discussed, clarified and adequately justified by the applicant. The CVMP acknowledged that statistically both studies showed non-inferiority of DRAXXIN as compared to tildipirosin and the results were considered sufficient to demonstrate efficacy of DRAXXIN in the proposed new indication.

4.2. Risk assessment

Antimicrobial resistance

The susceptibility distribution profile of *B. bronchiseptica* is mono-modal and no isolates were found resistant. No significant increase in resistance was observed towards already granted target pathogens, or foodborne pathogens and commensal organisms from the launch of DRAXXIN in 2003. It is unlikely that the addition of *B. bronchiseptica* to the indications will give rise to animal or public health concerns.

Environmental risk, user and target animal safety

The product is not expected to pose a risk to the environment, the user or the target animal when used according to the labelling.

4.3. Evaluation of the benefit-risk balance

Efficacy of DRAXXIN as **treatment** of SRD associated with *B. bronchiseptica* has been shown in two field studies run in Germany and Spain (A121-CDE-072 and A121C-ES-13-085). DRAXXIN was found to be non inferior to tildipirosin for the treatment of SRD associated with *B. bronchiseptica*, based on the day14 clinical cure rate. (Success rates of 93.7% and 98.9% on day14 respectively). Thus, DRAXXIN is accepted as an adequate treatment for the proposed indication.
Moreover, *B. bronchiseptica* is widely disseminated in pig herds. It spreads via (in)direct aerosol contact within a barn so animals co-housed with clinically diseased could be infected without showing clinical signs yet. Thus they should be treated at the same time to prevent further spreading of the disease (**metaphylaxis**).
No change to the impact on the environment is envisaged.
The benefit-risk balance remains unchanged.

5. Overall conclusions of the evaluation and recommendations

The CVMP considers by majority 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.

5.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

Annexes I and IIIB.