

Divergent position on a CVMP opinion on a type II variation to the terms of the marketing authorisation for DRAXXIN (EMEA/V/C/000077/II/0031)

Based on a favorable benefit-risk balance, the CVMP have adopted a positive opinion for the DRAXXIN type II variation application to add an additional pathogen, *Bordetella bronchiseptica*, to the existing indication (treatment and prevention of swine respiratory disease, SRD). The concerns that have led to enunciate a divergent opinion is that, although non-inferiority of DRAXXIN has been demonstrated as compared to tildipirosin in two pivotal field studies (one in Germany, one in Spain), the design and conduct of these field studies were not appropriate to demonstrate the efficacy of DRAXXIN in the treatment of SRD associated with *B. bronchiseptica*. Major shortcomings include the difficulties in establishing a proper diagnosis of SRD associated with *B. bronchiseptica* under the study conditions, the inadequacy of the combined clinical scoring system alone as primary efficacy variable, and the impact of concomitant diseases requiring additional treatments on the clinical signs of SRD and efficacy assessment.

In particular, it is noted that:

1. The diagnosis of *B. bronchiseptica* infection, accepted by the CVMP, was in both clinical studies based on clinical signs including coughing and sneezing which were considered typical for *B. bronchiseptica* infections, and the high isolation rate of this bacteria species from lavage samples from appr. 10% of treated animals. However, it is well established that *Bordetella bronchiseptica* can be found in the upper respiratory tract, even in clinically healthy animals, and no attempts were made by the applicant to confirm the etiological role of *B. bronchiseptica* in the SRD outbreak, e.g. by examination of lung samples or post treatment probes. Therefore, the role of *B. bronchiseptica* in the SRD outbreak remains unclear under these study conditions. Moreover, the undersigned are of the opinion that "coughing and sneezing", among other respiratory signs and depression is not typical for *B. bronchiseptica* alone but for any infectious respiratory disease in swine. Furthermore, it is noted that in the German field study a viral outbreak with Swine Influenza Virus was confirmed which required concomitant antipyretic treatment with an NSAID. From the data it is not clear whether this was a primary or co- infection as stated by the applicant and accepted by the CVMP. Hence, in the absence of further confirmatory diagnostic procedures, the role of *B. bronchiseptica* in this SRD outbreak could not be clearly identified.
2. The evaluation of the treatment responses based solely on a combined subjective scoring system of clinical signs is not appropriate in the absence of an objective parameter, such as rectal temperature. In both pivotal studies, treatment success and treatment failure have been assessed based on the absence and presence of coughing and sneezing, respectively. The combined scoring system does not allow for discriminating clinical signs, and "coughing and sneezing" is not typical (e.g. pathognomonic) for *B. bronchiseptica* infections as stated above. Additionally, "coughing and sneezing" is not an objective parameter, as claimed by the applicant and accepted by the CVMP, since the occurrence of "coughing and sneezing" was not monitored according to a predetermined standardized procedure. The undersigned are of the opinion that rectal temperature offers an objective measure of infectious diseases. Up to now in historical SRD field studies submitted in support of application for marketing authorization of veterinary medicinal products, rectal temperature was consistently included as a pivotal objective parameter together with a clinical scoring system. Thus, it is deemed not acceptable that rectal temperature was excluded from the efficacy assessment in the German study and was even not foreseen as an inclusion

criterion and efficacy parameter in the Spanish study. While it is acknowledged that a pure mono-infection with *B. bronchiseptica* does not necessarily induce pyrexia, an SRD outbreak does typically include pyrexia, even if associated with *B. bronchiseptica*. It is not acceptable to include animals without pyrexia for the claimed indication SRD. SRD is a multifactorial disease clinically associated with pyrexia and this clinical sign is next to other typical clinical signs as pre-conditions for treatments with an antimicrobial.

3. In the German field study, a viral outbreak with Swine Influenza Virus was diagnosed which required additional treatment with sodium salicylate. It can be assumed that the additional administration of a non-steroidal anti-inflammatory drug on study Day 2-4 had an impact not only on the course of rectal temperatures, but also (due to its anti-inflammatory properties) affects on respiratory signs. The clinical effect on the assessment parameter (SRD score) can, therefore, not be clearly related to the treatments with DRAXXIN and tildipirosin. Possible differences between the treatments groups could be masked by the concomitant treatments. To which extent such a masking might have happened cannot be evaluated since all animals received the concomitant treatments.
In both field studies pigs also suffered from diarrhea and concomitantly treated with colistin (DE, study Day 11-17) and colistin plus zinc oxide (ES, study Day 0-14). Although both drugs do not act systemically, an indirect impact on general clinical signs like depression (which can be related to SRD and diarrhea) cannot be excluded with certainty.
4. A further concern of the undersigned is that in the Spanish field study, the majority of pigs showed clinical signs of SRD but not pyrexia. Therefore, it is highly questionable if the administration of an antimicrobial, in particular a macrolide belonging to the group of critically important antimicrobials, was in line with responsible use principles for antimicrobials in this situation.

In conclusion, the undersigned are of the opinion that the efficacy of DRAXXIN in the treatment of SRD associated with *B. bronchiseptica* has not been demonstrated according to current scientific standards and, therefore, the benefit-risk balance is considered unfavorable.

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