Divergent position on a CVMP opinion on an Article 33(4) referral of Directive 2001/82/EC for

Florgane 300 mg/ml suspension for injection for cattle and pigs (EMEA/V/A/083)

CVMP was requested to give its opinion on whether the extension of the marketing authorisation for Florgane 300 mg/ml suspension for injection for cattle to the target species pigs should be granted.

The signers of this document find that that the documentation provided by the applicant is insufficient for approval of the extension because of the following observations.

- MIC\textsubscript{90} for \textit{Actinobacillus pleuropneumoniae} and \textit{Pasteurella multocida} is 0.5 and 1 µg/ml, but the official clinical break point set to ≤2 µg/ml. Florfenicol possesses a time-dependent activity and therefore is has to be present at the infection site at levels higher than the MIC for a certain time. \textit{A. pleuropneumoniae} bacteria can survive in macrophages and may maintain the infection if they are untouched by the antimicrobial. Since macrophages have a long turnover rate extracellular concentration has to be maintained during some days if the antibiotic in question is unable to kill the bacteria intracellularly. No information is available on the distribution of florfenicol to macrophages.

- Florgane 300 mg/ml at a single dose of 22.5 mg/kg leads to plasma concentration of florfenicol above 0.5 µg/ml for approximately 60 hours. One µg/ml may be covered for approximately 40 hours, whereas 2 µg/ml is not covered. Presuming that plasma concentration of florfenicol represents the concentration at infection site this means that Florgane at 22.5 mg/kg only can eradicate the most sensitive pathogens.

- Florgane 300 mg/ml is suspended in an aqueous base. In other florfenicol products the active is dissolved in organic solvents and these forms lead to somewhat higher plasma concentrations than Florgane 300 mg/ml when administered at a single dose\(^1\).

- The applicant has provided a dose titration study on experimentally infected animals with \textit{A. pleuropneumoniae} with a MIC of 0.5 µg/ml. The study shows an effect of all doses (7.5, 15, 22.5 and 30 mg/kg) compared to placebo but no dose effect relationship could be demonstrated. Due to a higher mortality in the 15 mg/kg group compared to the other treatment groups the applicant chose 22.5 mg/kg as the therapeutic dose. The dose titration study has several pitfalls including difference in clinical score between groups at treatment and an almost similar pattern in body temperature in the placebo group and the treated groups. The signers find that the dose titration study is not conclusive.

- In a field study involving 300 animals at 4 farms Florgane 300 mg/ml was compared with a control product also containing 300 mg florfenicol/ml. Florgane 300 mg/ml was tested at two doses 22.5 mg/kg and 30 mg/kg and the dose of the control product was 15 mg/kg twice with 48 hours apart. Nineteen animals were selected for necropsy before treatment

to confirm outbreak of acute pneumonia. Only 8 pathogens were isolated from these animals and in five isolates MIC was determined to 0.5 µg/ml. Treatment efficacy measured as cure rate was similar between Florgane and the control product. However, the minor change in body temperature after treatment in all groups suggests a mild infection. The signers find that the severity of the outbreaks has not been confirmed and the claim of acute respiratory disease is not demonstrated.

- General knowledge underlines that florfenicol has to be present at high concentrations at least for 4 days. This is not the case when administering Florgane at 22.5 mg/kg IM.

- The signers find that Florgane 300 mg/ml cannot fulfill the principles of responsible use of antimicrobial drugs as stated in the CVMP strategy on antimicrobials 2011-2015.

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