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

Nuflor Swine Once 450 mg/ml solution for injection (EMEA/V/A/080)

This referral under Article 33(4) of Directive 2001/82/EC was initiated due to concerns that the applicant had not satisfactorily demonstrated the clinical efficacy of Nuflor Swine Once 450 mg/ml solution for injection at a single intramuscular dose of 30 mg/kg bw in the treatment of swine respiratory disease. Concerns were raised about the high failure rate observed in the pivotal field study, the choice and dose of the positive control product used in that field study, the adequacy of the proposed single-dose administration and the increased potential for development of antimicrobial resistance.

It is the opinion of those undersigned that the data package presented in support of efficacy is in line with legislative requirements (Directive 2001/82/EC) and guideline recommendations (EMEA/CVMP/627/01-FINAL). Taking the totality of data presented, it can be accepted that there is sufficient evidence to support the efficacy of the Nuflor Swine Once at the dose of 30 mg/kg administered intramuscularly on a single occasion in the treatment of Swine Respiratory Disease associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis*. On this basis, the granting of the marketing authorisation for Nuflor Swine Once can be recommended.

With regard to the specific concerns raised, the following should be noted:

- **High cumulative relapse rate:** From a clinical perspective it is noted that the applicant choose strict inclusion criteria in the field study (i.e. the animals were at an advanced stage of disease at the time of treatment) and this may not reflect normal practice under field conditions where the treatment of swine respiratory disease would be initiated earlier. This may have contributed to the observed rate of failure/relapse. Failure rates did not correlate with the prevalence of one of the target bacteria species at the study sites, nor did they correlate with a low susceptibility of target bacteria species against florfenicol. In fact, the vast majority of pathogen strains isolated prior to treatment showed good susceptibility with MIC values of up to 0.5 µg/ml. None of the claimed bacterial pathogens isolated from failure animals showed a MIC > 0.5 µg/ml.

  While the exact cause of the apparent high rate of failure/relapse is unclear, it is accepted that Nuflor Swine Once was non-inferior to the reference product (enrofloxacin) for the primary efficacy variable. The mean failure rate in the clinical field study (day 11) was 20.7% in the Nuflor group and 27.3% in the control group, and was lower in the Nuflor group throughout the post treatment observation time. Whether a failure in one fifth of the treated animals is (too) high may be a subject of discussion; however, such a threshold has not been defined to date, and the rate of relapse was even higher in the authorised comparator product, which was used according to label. Indeed, for other procedures (e.g. Nuflor 300 mg/ml for Sheep), clinical efficacy studies with higher rates of relapse were accepted as pivotal data in support of efficacy. Variability of treatment results among different study sites in a European multi-centre field study is not

considered unusual (different aetiology, different disease pressure, different animal management practices, etc).

The reasons for apparent treatment failure and the variability in failure rates between study sites are not known and cannot be determined from this study. One theory proposed is that *A. pleuropneumoniae* may persist in alveolar macrophages and be liberated by the normal macrophage turn-over after some days, which could lead to re-infection. In order to be effective in this situation, it is suggested that florfenicol should be administered in accordance with a dosing regimen that will achieve a sufficient concentration in the extracellular environment until the *A. pleuropneumoniae* is liberated from the vesicles when the macrophages die. However, this is a hypothesis and is not verified by clinical data. Indeed, the argument that viable *A. pleuropneumoniae* can be liberated from viable alveolar macrophages after a period of days is not robustly substantiated. It is noted that Nuflor Swine Once proved to be effective in the treatment of experimental *A. pleuropneumoniae* respiratory disease in young pigs at all three doses tested (15, 30 or 45 mg/kg bw, respectively).

- **Choice and dose of the positive control used in that field study:** According to the legal provisions set in Annex I of Directive 2001/82/EC, a positive control product should be an authorised product according to current European legislation. No further guidance on the selection of an appropriate control product is included in the relevant CVMP guideline (EMEA/CVMP/627/01-FINAL). From a regulatory point of view, it is accepted that the reference product was an eligible comparator given that it is an authorised product according to the relevant European legislation, the claimed indication is similar to that proposed for Nuflor Swine Once and the dosage regimen used in the field study was in accordance with the label claim in the countries in which the field studies were conducted. No published or pharmacovigilance data indicate a lack of efficacy of the reference product when used according the label.

- **Single-dose administration:** The proposed treatment regimen is supported by the data package provided. Considering the MIC data from most recent isolates, obtained from pigs suffering from respiratory disease in the last 5 years florfenicol exhibited consistent MICs with MIC ranges of 0.06-1 µg/ml for each of *P. multocida* and *A. pleuropneumoniae*, and 0.125-0.5 µg/ml for *H. parasuis*. Regarding the critical issue of T>MIC, the majority of animals included in the pharmacokinetic studies show florfenicol plasma concentrations above 1 µg/ml for 48 hours (i.e. the time of re-dosing for Nuflor 300 mg/ml). Also, for the majority of animals, florfenicol plasma concentrations remain above 0.5 µg/ml for 72 hours. Efficacy of the proposed dose, relative to enrofloxacin (administered in accordance with label recommendations), was confirmed in the field.

- **Increased potential for development of antimicrobial resistance:** Several florfenicol formulations are currently authorised in the Community for use in pigs. Nuflor 300 mg/ml has been used for more than a decade in pigs in swine respiratory disease, yet resistance to florfenicol remains low among porcine respiratory pathogens. For the elimination phase of florfenicol in plasma, Nuflor Swine Once is comparable to Nuflor 300 mg/ml; therefore, florfenicol exposure to the target respiratory pathogens after administration of Nuflor Swine Once will be comparable to that achieved with the authorised product Nuflor 300 mg/ml. It is not expected, therefore, that the proposed dose of 30 mg florfenicol/kg administered intramuscularly as Nuflor Swine Once will increase the risk of resistance development, including for commensals, relative to the risk associated with dosing regimens currently authorised. This risk is considered to be low.

Taking the totality of data presented, the undersigned consider that the overall benefit-risk balance for Nuflor Swine Once 450 mg/ml solution for injection is positive.

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