Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, routes of administration, applicant in the Member States

Member State EU/EEA	Applicant	Name	Pharmaceutical form	Strength	Animal species	Route of administration
Belgium	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep - intramuscular
Denmark	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
France	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Germany	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Greece	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Ireland	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Italy	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular

Member State EU/EEA	Applicant	Name	Pharmaceutical form	Strength	Animal species	Route of administration
Luxembourg	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
The Netherlands	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Portugal	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
Spain	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep – intramuscular
United Kingdom	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor 300 mg/ml solution for injection for cattle and sheep	Solution for injection	300 mg/ml	Cattle and sheep	Cattle – subcutaneous and intramuscular Sheep - intramuscular

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Nuflor 300 mg/ml solution for injection for cattle and sheep

1. Introduction

Nuflor 300 mg/ml solution for injection for cattle and sheep contains florfenicol as active substance. Florfenicol is structurally related to thiamphenicol and has a similar pharmacological profile. The active substance is included in veterinary medicinal products currently licensed in several countries in the European Union for use in cattle and pigs for the treatment of respiratory disease. For sheep, the proposed indication is for treatment of respiratory tract infections due to *Mannheimia haemolytica* (*M. haemolytica*) and *Pasteurella multocida* (*P. multocida*) susceptible to florfenicol at a dose of 20 mg florfenicol/kg bodyweight intramuscular daily for three consecutive days.

The applicant Intervet International BV submitted an application for a decentralised procedure (DCP) for an extension (Article 19 of Regulation (EC) 1234/2008) of the existing marketing authorisation of Nuflor 300 mg/ml solution for injection for cattle to add sheep as a target species. The application was submitted to Ireland as reference Member State and Belgium, Denmark, France, Germany, Greece, Italy, Luxembourg, the Netherlands, Portugal, Spain and the United Kingdom as concerned Member States.

During the decentralised procedure two concerned Member States identified potential serious risks regarding the proposed indications (France) and the efficacy of the product (Denmark). These issues remained unsolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the CMD(v) was started. During the procedure the applicant provided additional data and the issues raised by France regarding the proposed indications were resolved. The concerns raised by Denmark remained unsolved and consequently the matter was referred to the CVMP on 21 September 2011.

The concerns raised for this referral procedure related to the efficacy of the product. Based on dossier data concerning Minimum Inhibitory Concentrations (MICs) for florfenicol (MIC_{90}= 1 µg/ml) and considering its pharmacokinetic/pharmacodynamic (PK/PD) plasma profile, the period of exposure to the MIC_{90} strength was believed by the objecting Member State to be too short. Furthermore, the treatment failure rates in the clinical field study submitted by the applicant were considered too high. For the objecting Member State, this gave rise to concerns that there was the potential for under-dosing and that there may be an increase in risk for development of florfenicol resistance.

2. Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant presented all available efficacy data for sheep.

Pharmacokinetics/pharmacodynamics data (PK/PD)

The adequacy of the treatment interval was one of the main points of discussion during the referral procedure. There was a concern that a dose of 20 mg florfenicol/kg administered intramuscularly every 24 hours would not maintain an active/effective concentration of florfenicol at the infection site for the between treatment interval (that is, 24 hours).

The applicant provided detailed pharmacodynamic and pharmacokinetic data to justify the proposed dose for the claimed indication. Those data can be summarised as follows:

- The MIC_{90} values of florfenicol are in the range 0.5 – 1 µg/ml for target pathogens *M. haemolytica* and *P. multocida*. The isolates on which the MIC data are based were collected from sheep with respiratory tract disease between 2006 and 2010.

- The following can be concluded from the pharmacodynamic data presented:
  - florfenicol has a pronounced bactericidal effect with Minimum Bactericidal Concentration (MBC) values the same, or one dilution higher, than the MIC of the tested strains. A florfenicol concentration of 4 x MIC (2 µg/ml) resulted in a decrease of bacterial count by 99.9% (3-Log drop) in 4 - 8 hours for the *M. haemolytica* isolates. Similarly, a florfenicol concentration of 2 x MIC (0.5-1 µg/ml) resulted in a 3-Log drop of bacterial count in 10 - 24 hours for the *P. multocida* isolates. From the *M. haemolytica* data, it can be seen that time to achieve a 3-Log reduction decreased with increasing florfenicol concentration; and,
  - after only two hours exposure, florfenicol exhibits a post-antibiotic effect (ranging from 1 - 3 hours at concentrations $\geq$1 µg/ml). The data suggest that if florfenicol concentrations in plasma/tissue are above the MIC for in excess of two hours, there is likely to be a marked post-antibiotic effect.
- Although some concentration dependency trends were observed for *M. haemolytica* strains, the killing effect/kinetic does not increase dramatically with the concentration of the antibiotic over the MIC or twice the MIC. Thus, florfenicol behaves essentially like a bactericidal time dependant antibiotic. The available data suggest, therefore, that for this antibiotic the most relevant parameter for prediction of efficacy is time above MIC.
- Based on data generated in the pivotal pharmacokinetic study, intramuscular administration of the proposed recommended treatment dose resulted in mean peak serum concentrations of ~9 - 10 µg/ml by approximately 1 hour after treatment. Elimination half-life was estimated to be 13.76 $\pm$ 6.42 hours. Repeat administration of 20 mg/kg once daily for three days (proposed posology) resulted in some accumulation (accumulation factor of 1.48). Mean florfenicol concentration in serum remained above 1 µg/ml (MIC_{90}) for up to 18 hours following administration of the product at the recommended treatment dose.
- A variety of studies are available on the distribution of florfenicol in bronchial secretions in man and various animal species (pigs and calves). Based on available data, it would appear that florfenicol concentrations achieved in lung tissue/bronchial secretions are at least as high as those detected in serum. While similar data have not been generated for sheep, it is reasonable to assume that that florfenicol concentrations achieved in plasma reflect what will be achieved in the lung.

The CVMP accepted that the MIC and pharmacokinetic data, taken together with what is known about florfenicol kill kinetics and post-antibiotic effect (PAE), support the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 µg/ml and suggest that the proposed dose of 20 mg florfenicol/kg and the proposed between treatment interval of 24 hours should be appropriate for testing in the clinical setting for the treatment of respiratory infection associated with *M. haemolytica* and *P. multocida*. It is noted that, currently, for ovine respiratory disease pathogens there is no internationally agreed breakpoint for florfenicol sensitivity. (Clinical breakpoint is a MIC value used by clinicians to classify bacteria as susceptible or resistant to a certain antimicrobial and is therefore a measure of clinical efficacy.)

Dose finding study

In support of the proposed recommended treatment dose, the applicant conducted a comprehensive dose finding study using an experimental model of respiratory disease where test animals were challenged with *M. haemolytica*. The results of this study demonstrated that florfenicol administered once daily at a dose of either 10, 20 or 30 mg/kg was effective for the treatment of pneumonia in sheep induced by *M. haemolytica*. Linear trend analyses of Day 4 and Day 6 rectal temperature data (primary variable) suggest that a dose response plateau was achieved at the florfenicol 20 mg/kg dosage. Secondary variables (e.g. mortality, pathogen recover, lung weight, lesion weight) confirm

that 20 mg/kg is superior to a dose of 10 mg/kg. There appears to be no advantage to increasing the dose to 30 mg/kg.

The selected dose and between treatment interval was in line with the PK/PD conclusions. Based on the available pharmacodynamic data, it is accepted that a dose selected on the basis of this study should also be predictive of likely efficacy against *P. multocida*.

Field study

The applicant conducted a single field study to determine the efficacy and safety of the test product administered at 20 mg florfenicol/kg bodyweight intramuscularly once daily for three days to sheep with naturally acquired respiratory infections. The study was conducted at multiple sites in Germany and Spain. In terms of design, the field study followed EMA/CVMP guideline recommendations. Based on the findings of the field study, the applicant concluded that based on the primary efficacy parameter – treatment failure rates, Nuflor can be considered superior (at Day 4) or non-inferior (at Day 11) to the positive control product containing 100 mg/ml oxytetracycline, when used for the treatment of respiratory disease in sheep associated with either *M. haemolytica* or *P. multocida*. The conclusions of the study are accepted. While there were some reservations about the use of oxytetracycline as the positive control, it is accepted that the chosen comparator product has a claim for ovine respiratory disease and is commonly used as a first-line therapy that will most likely be administered without any information on the sensitivity of causal organisms. Therefore, its use as the positive control is in line with existing guidance and is considered legitimate.

Conclusion

Having considered all data submitted in writing and in the oral explanation provided by the applicant the CVMP concluded that the available data are adequate to support the efficacy of Nuflor 300 mg/ml solution for injection for cattle and sheep at the dose of 20 mg/kg daily via the intramuscular route of administration for three consecutive days in the treatment of Ovine Respiratory Disease associated with *M. haemolytica* and *P. multocida*. However, the CVMP agreed that section 4.9 of the Summary of Product Characteristics should be amended to clarify that the recommended treatment dose and treatment interval for sheep is based on the time mean florfenicol concentrations are maintained above MIC90 (see Annex III).

3. Benefit-risk assessment

Introduction

Nuflor 300 mg/ml solution for injection for cattle and sheep contains florfenicol as active substance. Florfenicol is structurally related to thiamphenicol and has a similar pharmacological profile. The active substance is included in veterinary medicinal products currently licensed in several countries in the in the European Union for use in cattle and pigs for the treatment of respiratory disease.

The application in question, submitted via the decentralised procedure, is an extension of the existing marketing authorisation of Nuflor 300 mg/ml solution for injection for cattle to add sheep as a target species.

Direct therapeutic benefits

The benefit of florfenicol is that ovine respiratory disease associated with susceptible *M. haemolytica* and *P. multocida* can effectively be treated.

Additional benefits

None.

Risk assessment

Quality, User safety, Environmental risk and Residues were not assessed in this referral procedure.

Target animal safety

This part of the dossier was not assessed in this referral procedure as no concern was notified by the reference Member State nor was any concern raised during the procedure as the dose remains as proposed and concluded by the reference Member State.

Risk management or mitigation measures

The warnings in the product literature remain appropriate with the change indicated in section 2.4 below. No further risk management or mitigation measures are required as a consequence of this referral procedure. The concern relating to the high failure rate and assumed lack of efficacy has been addressed under benefit assessment.

Evaluation of the benefit-risk balance

Overall, the benefit-risk balance is considered positive for Nuflor 300 mg/ml solution for injection for cattle and sheep. The concern related to the efficacy of the product – in particular to the high failure rate – have been assessed and it is confirmed that the product is proved to be efficacious in the treatment of ovine respiratory disease associated with *M. Haemolytica and P. multocida* when administered at a dose of 20 mg/kg bodyweight once daily via the intramuscular route of administration for three days.

Conclusion

Based on the data presented in relation to the concerns notified for this referral procedure, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the benefit-risk balance was favourable.

Grounds for amendment of the summary of product characteristics

Having considered all data submitted in writing and in the oral explanation the CVMP concluded that:

- The MIC and pharmacokinetic data, taken together with what is known about florfenicol kill kinetics and post-antibiotic effect, support the recommended treatment interval (24 hours) for target respiratory tract pathogens with MIC up to 1 µg/ml when the product is administered to sheep at the proposed dose of 20 mg florfenicol/kg bodyweight,
- The proposed dosing schedule is supported by a dose finding study using an experimental model of respiratory disease where test animals were challenged with *Mannheimia haemolytica*, and
- A field study conducted in line with EMA/CVMP guideline recommendations showed that Nuflor, administered in accordance with the proposed dosing schedule, was non-inferior to the authorised

reference product, Terramycin 100 mg/ml, when used for the treatment of respiratory disease in sheep associated with either *Mannheimia haemolytica* or *Pasteurella multocida*.

The overall conclusion is that the efficacy dataset as a whole is adequate to support the efficacy of Nuflor 300 mg/ml solution for injection for cattle and sheep at the dose of 20 mg/kg daily via the intramuscular route of administration for three consecutive days in the treatment of Ovine Respiratory Disease associated with *M. haemolytica* and *P. multocida*. However, the CVMP agreed that section 4.9 of the Summary of Product Characteristics should be amended to clarify that the recommended treatment dose and treatment interval for sheep is based on the time mean florfenicol concentrations are maintained above MIC_{90}.

Therefore, the CVMP concluded that the objections raised by Denmark should not prevent the granting of the marketing authorisation for Nuflor 300 mg/ml solution for injection for cattle and sheep as the overall benefit-risk balance of the product is positive, subject to the recommended changes in the product information set out in annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

The valid Summary of Product Characteristics, Labelling and Package Leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of Product Characteristics

4.9 Amounts to be administered and administration route

…….

Sheep:

……

Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 µg/ml) for up to 18 hours after administration of the product at the recommended treatment dose. The pre-clinical data provided support the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 µg/ml.

Package leaflet

8. DOSAGE FOR EACH SPECIES, ROUTES AND METHOD OF ADMINISTRATION

…….

Sheep:

……

Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 µg/ml) for up to 18 hours after administration of the product at the recommended treatment dose. The pre-clinical data provided support the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 µg/ml.