Annex I

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

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Austria[1]	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Belgium	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Bulgaria[1]	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Cyprus	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Czech Republic	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Denmark	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	PigFlor Once	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Estonia	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular

[1] Marketing authorisation granted

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
France[1]	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Germany[1]	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Greece	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Hungary	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Ireland	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Italy	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	NUFLOR Suini One, 450 mg/ml soluzione iniettabile per suini	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Latvia	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Lithuania	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Luxembourg	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Malta	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
The Netherlands	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Poland	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Portugal	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Romania[1]	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Slovakia	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Slovenia	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
Spain	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Flomac porcino dosis única 450 mg/ml solución inyectable	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular
United Kingdom	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Nuflor Swine Once 450 mg/ml solution for injection	florfenicol	Solution for injection	450 mg/ml	Pigs	Intramuscular

Annex II

Scientific conclusions and grounds for refusal of the granting of the marketing authorisations

Overall summary of the scientific evaluation of Nuflor Swine Once 450 mg/ml solution for injection

1. Introduction

Nuflor Swine Once 450 mg/ml solution for injection contains florfenicol as active ingredient. 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 diseases. This product is intended for use in pigs for the treatment of respiratory infections caused by strains of *Actinobacillus pleuropneumoniae*, *Haemophilus parasuis* and *Pasteurella multocida* susceptible to florfenicol. The proposed dose is 30 mg florfenicol/kg bodyweight given by intramuscular administration as a single injection.

The applicant submitted an application for a decentralised procedure for Nuflor Swine Once 450 mg/ml solution for injection. This is a 'hybrid application' according to Article 13(3) Directive 2001/82/EC, as amended, referring to the reference product, Nuflor Swine 300 mg/ml solution for injection (FR/V/0118/001). Nuflor Swine Once 450 mg/ml solution for injection differs from the reference veterinary medicinal product by a higher concentration of active substance, single administration, a change in therapeutic indication but also by a different co-solvent. The application was submitted to Germany as reference Member State and Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom as concerned Member States.

Potential serious risks were identified during the decentralised procedure by Denmark regarding the high failure rate observed in the pivotal clinical field trial and potential for development of antimicrobial resistance to florfenicol. These issues remained unsolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the CMD(v) was started. The Member States concerned failed to reach an agreement regarding the product and consequently the matter was referred to the CVMP on 19 December 2011.

This referral under Article 33(4) of Directive 2001/82/EC was made 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 have been raised about the high failure rate observed in the pivotal field study and the choice and dose of the positive control product used in that field study. Also, the principle of single-dose administration had been questioned in terms of the sustained concentration above the Minimum Inhibitory Concentration (MIC) and the increased potential for development of antimicrobial resistance.

On 13 June 2012 the CVMP adopted an opinion regarding this referral. The opinion recommended the granting of the marketing authorisation for Nuflor Swine Once 450 mg/ml solution for injection, subject to a condition to provide further efficacy data. On 31 August 2012, during the written phase of the Standing Committee procedure, the Netherlands submitted an objection to the opinion adopted by CVMP on 13 June 2012. On 27 September 2012 a plenary meeting of the Standing Committee on Veterinary Medicinal Products took place. The Standing Committee noted that there are serious uncertainties in CVMP's opinion on Nuflor Swine Once 450 mg/kg solution for injection in relation to the benefit-risk assessment, in particular regarding the efficacy of the product and the appropriate dosing. The Standing Committee noted that the CVMP recommended the granting of the marketing authorisation of the product subject to a condition requesting further clinical data on the efficacy of the veterinary medicinal product. In view of the uncertainties and lack of data, the Standing Committee

concluded that the CVMP should reconsider the opinion and evaluate again the benefit-risk balance of Nuflor Swine Once 450 mg/kg solution for injection. On 3 October 2012 the European Commission sent a letter to the CVMP requesting a reconsideration of the opinion adopted on 13 June 2012.

It should be noted that since the commencement of this referral procedure, marketing authorisations for Nuflor Swine Once 450 mg/ml solution for injection have been granted in Austria, Bulgaria, France, Germany and Romania.

2. Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant presented all available efficacy data for Nuflor Swine Once 450 mg/ml solution for injection. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from Germany.

2.1. Relevance of the choice of positive control product

The choice of the selected positive control product and its dosing regimen were considered by the Committee, as well as whether it is appropriate to compare a time-dependent antimicrobial (florfenicol) and a concentration-dependent antimicrobial (enrofloxacin).

According to the legal provisions set out 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, e.g. time-dependent versus concentration-dependent antimicrobials is included in the relevant guideline EMEA/CVMP/627/01-FINAL. The CVMP noted that the reference product (Enrofloxacin 5% solution for injection) is an authorised product according to the relevant European legislation, and the dosage regimen used in the field study was in accordance with the label claim in the countries of the field studies.

The applicant submitted a multicentre randomised controlled field study including a total of seven study sites in Spain, Germany and France to confirm the efficacy and field safety of Nuflor Swine Once 450 mg/ml solution for injection in the treatment of swine respiratory disease associated with *A. pleuropneumoniae, P. multocida* and *H. parasuis*. The study was well conducted and according to current scientific standards. Enrofloxacin 5% solution for injection was used for control. Clinical efficacy was assessed based on mean cumulative failure rates on Day 5 and Day 11 post-treatment. The mean cumulative failure rate for Nuflor Swine Once 450 mg/ml solution for injection in this field study was 8.9% on Day 5 and 20.7% on Day 11. For the reference product mean cumulative failure rates were 13.5% and 27.3% on Day 5 and Day 11, respectively. Based on these results, Nuflor Swine Once 450 mg/ml solution for injection at a single intramuscular dose of 30 mg/kg bodyweight proved to be non-inferior to the positive control enrofloxacin 5% solution for injection.

Nevertheless, the major concern of the Committee is the high variability of the failure rates in the clinical field study on Day 11 after treatment (primary endpoint). Seven sites in three countries have been investigated. The mean failure rate at Day 11 is 20.7% and 27.3% for Nuflor Swine Once and the comparator, respectively, but a large variation was observed between sites. The failure rate for Nuflor Swine Once varied from 0 to 56% at Day 11 and was similar to the comparator enrofloxacin with 0 to 42%. The dose of enrofloxacin was 2.5 mg/kg IM for 3 days according to the label. It is well known that a dose of enrofloxacin of 2.5 mg/kg does not follow the current knowledge of the optimal dosing for a fluoroquinolone, which requires high doses of 5 mg/kg for a treatment period of 3-5 days. These higher doses and duration of treatment are authorised in a number of EU Member States, e.g. Denmark, the Netherlands and the United Kingdom.

2.2. Correlation between plasma concentrations and pulmonary concentrations or high failure rate

The Committee considered whether the plasma concentrations of Nuflor Swine Once 450 mg/ml solution for injection, when corrected for plasma protein binding, adequately correlate to pulmonary concentrations (e.g. target site) and whether this explains the high failure rate.

No robust information is available about the distribution of florfenicol to the site of infection. Based on the available pharmacokinetic data in swine and limited experiments in other species it is reasonable to predict that florfenicol concentrations may be equal at the level as in plasma. *A. pleuropneumoniae* is the only organism out of the three target pathogens which is taken up by alveolar macrophages and stored intracellularly in vesicles and possibly gives rise to a re-infection when the macrophages die. This would mean that an efficient antibiotic either has to penetrate to the site of *A. pleuropneumoniae* storage (i.e. macrophages vesicles) or to be maintained in a sufficient concentration in the extracellular environment until the *A. pleuropneumoniae* is liberated from the vesicles when the macrophages die.

The reasons for the observed large variation of failure rates in the clinical field study are not known and cannot be determined from this study, nor on basis of other data presented during this referral procedure. The persistence of *A. pleuropneumoniae* in alveolar macrophages might be one possible explanation for these results, but is not verified by clinical data.

2.3. Duration of effect

The Committee considered whether there is an appreciable "post-antibiotic effect", as well as intracellular effects, that can justify this long acting preparation, since plasma concentrations may not be maintained above MIC for the treatment period.

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*. Florfenicol is bacteriostatic and exerts time-dependent activity.

Post-antibiotic effect and post-antibiotic sub inhibitory effect against florfenicol were observed for three *P. multocida* and three *A. pleuropneumoniae* strains with a MIC of 0.5 µg/ml *in vitro*. Theoretically, the ability of an antibiotic to induce a post-antibiotic effect is an attractive property since antibiotic concentrations could fall below the MIC for the bacterium and yet retain their effectiveness in their ability to suppress bacterial growth. However, the role of post-antibiotic effect in terms of efficacy is disputable and no firm conclusions with regard to effect duration can be drawn.

Pharmacokinetic/pharmacodynamic models using the raw data provided by the applicant could give another explanation for the different treatment failure rates in the clinical field study. Nuflor Swine Once per se is not a classic long acting preparation and a single dose of 30 mg/ml is considered not sufficient to treat respiratory tract infections where some pathogens have a MIC of 1 µg/ml.

2.4. Relevance of the dose for the development of antimicrobial resistance

The Committee considered whether the proposed dose of 30 mg/kg bw intramuscularly once may lead to a long sub-therapeutic period (e.g. below the MIC) and thus to development of florfenicol resistance.

Pharmacokinetic data suggest that the elimination of the active ingredient is independent of the formulation and the dosage as long as the absorption phase is completed. However, no

pharmacokinetic data of the terminal phases are available which could allow for a robust comparison between Nuflor Swine Once 450 mg/ml solution for injection and conventional formulations in regard to duration of sub-therapeutic concentrations. Thus, the impact on development of florfenicol resistance when used in the proposed dose of 30 mg/kg bw IM once compared to authorised dosing regimens can hardly be estimated. Whether the risk for the rate of resistance development would be dependent on the dose in this case is not possible to conclude on based on available data. Notwithstanding, Nuflor Swine Once 450 mg/ml solution for injection at the proposed posology cannot fulfil the principles of responsible use of antimicrobials as stated in the CVMP strategy on antimicrobials 2011-2015 due to concerns for lack of efficacy.

3. Benefit-risk assessment

Nuflor Swine Once is indicated for the treatment of swine respiratory disease associated with susceptible *Actinobacillus pleuropneumoniae, Haemophilus parasuis* and *Pasteurella multocida* at a single intramuscular dose of 30 mg/kg bodyweight. However, the efficacy could not be clearly confirmed in the pivotal multicentre randomised controlled field study. Treatment of acute respiratory tract infection in pigs with Nufor Swine Once at a single intramuscular dose of 30 mg/kg bw revealed high failure rates at Day 11 after treatment. Seven sites in three countries have been investigated. The mean failure rate at Day 11 was 20.7% and 27.3% for Nuflor Swine Once and the reference product (Enrofloxacin 5% solution for injection), respectively, but a large variation in the failure rates at Day 11 from 0 to 56% was observed between sites. Such high variations in failure rates reveal the risk of insufficient clinical efficacy and thus, represent an animal welfare concern.

The reasons for these observations are not known and cannot be determined from this study, nor on basis of other data presented during this referral procedure. One explanation for the high failure rate of Nuflor Swine Once may be the short duration of active concentration at the infection sites. Infection sites for the pathogens in question include bronchial epithelia lining fluid, bronchial epithelium and alveolar macrophages. No information is available about the florfenicol distribution to these sites in pigs but limited experiments in other species indicate that the concentration may be approximately similar to the concentration in plasma.

Several studies reveal that the MIC value for *A. pleuropneumoniae* and *P. multocida* vary from 0.25 to 1 µg/ml with MIC_{90} of 0.5 µg/ml. In the field studies some isolates show a MIC of 1 µg/ml. The official clinical break point for florfenicol sensitivity is ≤2 µg/ml. As the activity of florfenicol is time dependent, the active concentration has to be above MIC for a certain time. Nuflor Swine Once at a single dose of 30 mg/kg bw IM leads to plasma concentration of florfenicol above 0.5 µg/ml for about 72 hours. For approximately 36 hours 1 µg/ml may be covered, whereas 2 µg/ml is covered only for a very short time.

The CVMP therefore considers that Nuflor Swine Once cannot fulfil the principles of responsible use of antimicrobials and concludes that the benefit-risk balance is negative.

Conclusion

Having considered all the data submitted in writing and in the oral explanations the CVMP concluded that the observed high and variable clinical failure rates in the clinical field study on Day 11 post-treatment are considered unacceptable. In addition, it cannot be ruled out that a single intramuscular dose of 30 mg/kg bw of this time-dependent antimicrobial may not be sufficient to treat respiratory tract infections, in particular when pathogens are associated with MIC values ≥1 µg/ml.

Therefore, the CVMP concluded that the overall benefit-risk balance is negative and recommends the refusal of the granting of the marketing authorisation for Nuflor Swine Once 450 mg/ml solution for injection and the suspension of the existing marketing authorisations (see Annex I).

Grounds for refusal of the granting of the marketing authorisations

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

- the observed high and variable clinical failure rates in the clinical field study on Day 11 post-treatment are considered unacceptable;
- it cannot be ruled out that a single intramuscular dose of 30 mg/kg bw of this time-dependent antimicrobial may not be sufficient to treat respiratory tract infections, in particular when pathogens are associated with MIC values ≥1 µg/ml;

and the application does not satisfy the criteria for authorisation in respect of efficacy. Therefore the CVMP recommends the refusal of the granting of the marketing authorisations for Nuflor Swine Once 450 mg/ml solution for injection and associated names and the suspension of the existing marketing authorisations.

Annex III

Condition for lifting the suspension of the marketing authorisations

National Competent Authorities, coordinated by the reference Member State, shall ensure that the following condition is fulfilled by the marketing authorisation holder:

The marketing authorisation holder should reconsider the selection of the treatment dose and should provide further clinical data to confirm the efficacy of the intended dosage in the treatment of Swine Respiratory Disease associated with the target pathogens *A. pleuropneumoniae*, *P. multocida* and *H. parasuis* under field conditions.

The marketing authorisation holder should provide a GCP-compliant clinical field study. This should include sufficiently large number of target animals to ensure the validity of the results in terms of both clinical relevance and statistical significance. The design of the field study should follow the design of the field study V-0049-0059 in terms of the inclusion/exclusion criteria and clinical endpoints. It is important to confirm the aetiology of the disease by sampling a sufficient number of study animals at each study site prior to treatment, preferably by trans-tracheal lavage, and present susceptibility data of both Nuflor Swine Once and the control product. A positive control product should be used for comparison in a non-inferiority design. This control should preferably belong to a different class of antimicrobials for which sufficient efficacy has been demonstrated, e.g. tulathromycin.