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	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml Injektionssuspension für Rinder und Schweine	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Belgium	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspensie voor injectie voor runderen en varkens	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Bulgaria	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml инжекционна суспензия за говеда и прасета	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Czech Republic	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml injekční suspenze pro skot a prasata	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Denmark	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml, injektionsvæske, suspension til kvæg og svin	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
France[1]	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspension injectable pour bovins et porcins	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Germany[1]	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml Injektionssuspension für Rinder und Schweine	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular

[1] Marketing authorisation granted

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Greece	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml Ενέσιμο εναιώρημα για Βοοειδή και χοίρους	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Hungary	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml injekció szarvasmarha és sertés részére A.U.V.	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Ireland	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspension for injection for cattle and pigs	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Italy	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml sospensione iniettabile per bovini e suini	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Lithuania	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml injekcinė suspensija galvijams ir kiaulėms	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Luxembourg	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 Mg/Ml suspension injectable pour bovins et porcins	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
The Netherlands	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspensie voor injectie voor runderen en varkens	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Poland	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml, zawiesina do wstrzykiwań dla bydła i świń	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Portugal	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspensão injectável para bovinos e suínos	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Romania	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspensie injectabilă pentru bovine şi porcine	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Slovakia	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml injekčná suspenzia pre hovädzí dobytok a ošípané	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
Spain[1]	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspensión inyectable para bovino y porcino	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular
United Kingdom	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Florgane 300 mg/ml suspension for injection for cattle and pigs	florfenicol	Suspension for injection	300 mg/ml	Cattle and pigs	Intramuscular

Annex II

Scientific conclusions and grounds for the granting of the extension of the marketing authorisation for Florgane 300 mg/ml suspension for injection for cattle to the target species pigs

Overall summary of the scientific evaluation of Florgane 300 mg/ml suspension for injection for cattle and pigs

Introduction

Florgane 300 mg/ml suspension for injection contains florfenicol as active ingredient. Florfenicol is structurally related to thiamphenicol and has a similar pharmacological profile.

The applicant submitted an application for a decentralised procedure for Florgane 300 mg/ml suspension for injection for cattle and pigs and associated names. This application is an extension to add pigs as a target species to the existing 300 mg florfenicol/ml suspension for injection product authorised for use in cattle. Florgane 300 mg/ml suspension for injection has been authorised for use in cattle as a hybrid of Nuflor 300 mg/ml solution for injection using the decentralised procedure with Germany as a reference Member State and Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Greece, Hungary, Ireland, Italy, Lithuania, Luxemburg, the Netherlands, Poland, Portugal, Romania, Slovakia, Spain and the United Kingdom as concerned Member States.

The intended use in pigs is for the treatment of respiratory infections caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol. The proposed dose is 22.5 mg florfenicol/kg body weight given by intramuscular administration as a single injection.

This extension application was submitted as a decentralised procedure under Article 13(3) of Directive 2001/82/EC, as amended, to the above-mentioned Member States as for the initial application for cattle. The reference product was Nuflor Swine Injectable Solution 300 mg/ml.

During the decentralised procedure potential serious risks were identified by Denmark regarding the sustained concentration above the Minimum Inhibitory Concentration (MIC) at the site of infection for the necessary duration. These issues remained unsolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD(v)) was started. The Member States concerned failed to reach an agreement in respect of the extension of the marketing authorisation of Florgane 300 mg/ml suspension for injection for cattle to the target species pigs and consequently the matter was referred to the CVMP on 19 April 2012.

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 Florgane 300 mg/ml suspension for injection at a single intramuscular dose of 22.5 mg/kg bw in the treatment of swine respiratory disease.

Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant presented all available efficacy data for Florgane 300 mg/ml suspension for injection for the target species pigs. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from Germany.

Duration of effect

The Committee considered whether the duration of efficacious concentrations lasting less than 2 days after a single application is considered sufficient for treatment of severe respiratory diseases caused by *A. pleuropneumoniae* and *P. multocida* in pigs.

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_{90} ranges of 0.25-1 µg/ml for

A. pleuropneumoniae and 0.5 µg/ml for *P. multocida*. Florfenicol is bacteriostatic and exerts time-dependent activity.

Since florfenicol per definition is a time-dependent antimicrobial, T>MIC is the most appropriate pharmacokinetic/pharmacodynamic surrogate. However, no evidence based data are available on how long the time over the MIC should be for florfenicol and swine respiratory disease related target organisms. This applies to both the duration of time necessary to be above the MIC within an entire dosing interval and to the total number of subsequent dosing(s) needed for efficacious treatment. Thus, pharmacokinetic/pharmacodynamic analyses can provide approximation for dose finding only and clinical studies are essential to confirm a proposed dosing scheme.

Based on a GLP-compliant dose titration study using pigs artificially infected with *A. pleuropneumoniae* two doses of florfenicol were selected for further evaluation in a clinical field study, which was supported by pharmacokinetic/pharmacodynamic analysis.

In a GCP-compliant randomised blinded controlled clinical field study Florgane 300 mg/ml proved to be non-inferior in the treatment of swine respiratory disease associated with *A. pleuropneumoniae* and *P. multocida* at both single IM doses of 22.5 mg/kg and 30 mg/kg bw when compared to a control product containing 300 mg florfenicol/ml administered at a dose of 15 mg/kg bw IM twice 48 hours apart. The pigs enrolled in the study were suffering from mild to moderate respiratory disease which is considered consistent with the field situation where animals are treated as early as possible before signs of swine respiratory disease become severe. The dose of 30 mg/kg did not prove additional benefit in relation to efficacy compared to the dose of 22.5 mg/kg bw, therefore the latter is justified as recommended treatment dose.

Relevance of the dose for the development of antimicrobial resistance

The Committee considered whether the proposed dose of 22.5 mg/kg IM once may lead to a long sub-therapeutic period (e.g. below MIC) and thus to development of florfenicol resistance.

Resistance to florfenicol remains very low among porcine respiratory pathogens whereas the active substance has been used for more than one decade in pigs in swine respiratory disease. Plasmid mediated resistance has only been scarcely identified among porcine respiratory pathogens without indication of spreading. The use of florfenicol in pigs has not generated any significant resistance of the target pathogens. 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 Florgane 300 mg/ml suspension 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 22.5 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.

Benefit-risk assessment

Introduction

Florgane 300 mg/ml suspension 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.

The application in question, submitted via the decentralised procedure, is a so called “hybrid application” according to Article 13(3) of Directive 2001/82/EC. The reference veterinary medicinal product is Nuflor Swine Injectable Solution 300 mg/ml. Florgane 300 mg/ml suspension for injection differs from the reference veterinary medicinal product by a single administration, a different pharmaceutical form and composition.

The product is presented in four multidose vial sizes of 50 ml, 100 ml, 250 ml and 500ml.

Direct therapeutic benefit

Swine respiratory disease is one of the most important diseases of pig production resulting from infection of susceptible pigs with virus and obligatory and facultative pathogenic bacteria, which require effective therapeutic treatment.

The benefit of Florgane 300 mg/ml suspension for injection is that swine respiratory disease associated with susceptible *Actinobacillus pleuropneumoniae and Pasteurella multocida* can be treated. The product proved to be non-inferior to an established control product containing florfenicol which is administered twice 48 hours apart.

Indirect or additional benefits

A single-dose therapy of the individual animal has advantages (less work for the user, fewer treatment errors, less handling of pigs leading to less stress) over a multi-dose therapy and/or oral group therapy.

Risk assessment

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

Resistance

Resistance to florfenicol remains very low among porcine respiratory pathogens while Nuflor Swine Injectable Solution 300 mg/ml has been used for more than one decade in pigs in swine respiratory disease. For the claimed bacteria species good susceptibility against florfenicol with MIC_{90} valules for *P. multocida* and *A. pleuropneumoniae* of 0.5 µg/ml was determined.

Plasmid mediated resistance has only been scarcely identified among porcine respiratory pathogens without indication of spreading. The use of florfenicol in pigs has not generated any significant resistance of the target pathogens. Florgane 300 mg/ml will not differ from the previous florfenicol formulations as far as the plasma elimination phase and sub-therapeutic periods are concerned.

Risk management or mitigation measures

The warnings in the product literature remain appropriate. No further risk management or mitigation measures are required as a consequence of this referral procedure.

Evaluation and conclusion on the benefit-risk balance

Overall, the data package submitted by the applicant is considered sufficient taking into account the nature of this application for an extension of the marketing authorisation (hybrid application). In conclusion, the benefit-risk ratio is considered positive for Florgane300 mg/ml suspension for injection for cattle and pigs.

Grounds for the granting of the extension of the marketing authorisation for Florgane 300 mg/ml suspension for injection for cattle to the target species pigs

Whereas:

- the CVMP reviewed all available data submitted by the applicant to support the use of the product in the target species pigs for the treatment of respiratory infections caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol at the dose of 22.5 mg florfenicol/kg body weight given by intramuscular administration as a single injection;
- the data package submitted by the applicant is considered sufficient taking into account the nature of this application for an extension of the marketing authorisation (hybrid application);
- it is considered there is no increase in the risk of development of antimicrobial resistance;

The overall conclusion is that that the efficacy dataset as a whole is adequate to support the efficacy of the product in target species pigs at the dose of 22.5 mg florfenicol/kg body weight given by intramuscular administration as a single injection for the treatment of respiratory infections caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol.

Therefore, the CVMP recommended the granting of the extension of the marketing authorisation to the target species pigs for the veterinary medicinal products referred to in annex I for which the valid Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in annex III.

Annex III

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.