Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Florgane 300 mg/ml

Suspension for Injection for Cattle and Pigs

Date: 11 July 2013

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0132/001/DC
Name, strength and pharmaceutical form	Florgane 300 mg/ml Suspension for Injection
Applicant	Emdoka bvba John Lijsenstraat, 16, B-2321 Hoogstraten, Belgium
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Cattle, Pig
Indications for use	Cattle: Preventive and therapeutic treatment of respiratory tract infections in cattle caused by florfenicol susceptible Mannheimia haemolytica, Pasteurella multocida and Histophilus somni. The presence of the disease in the herd should be established before treatment. Pigs: Treatment of acute outbreaks of respiratory disease caused by strains of Actinobacillus pleuropneumoniae and Pasteurella multocida susceptible to florfenicol.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended
Date of completion of the original Decentralised procedure	23.03.2010
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	AT, BE, BG, CZ, DK, EL, ES, FR, HU, IE, IT, LT, LU, NL, PL, PT, RO, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains Florfenicol 300 mg/ml and n-Butanol, Potassium metabisulphite (E224), Carmellose sodium, Povidone K 12, Lecithin (Soybean

origin), Sodium citrate, Potassium dihydrogen phosphate, Magnesium gluconate, and Water for injection.

The product is packed in semi-transparent, sterile, polypropylene multi-dose bottles of 50 ml, 100 ml, 250 ml or 500 ml with sterile fluorinated bromobutyl rubber stoppers. Each bottle is closed with a sterile aluminium cap with or without flip-off cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is florfenicol, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products (pharmaceuticals)

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at +25 ± 5 °C.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Additional information on testing instructions is provided in this section.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a hybrid application according to Article 13 (3), in which reference is made to “Nuflor injectable solution 300 mg/ml” in the original dossier for authorization in cattle and to “Nuflor Swine Injectable solution 300 mg/ml” in the extension dossier for the food-producing species pig. Both Nuflor products (Schering-Plough Animal Health) have the same composition. The product differs from the reference veterinary medicinal products through its pharmaceutical form but also through a different posology. Product-related bridging data were submitted in the respective Parts III.A for user safety and for safety to the environment (ERA). For product-related animal safety reference was made to the respective Parts IV.I.B.

III.A Safety Testing

Pharmacological Studies

See Part IV A (Pre-Clinical Studies)

Toxicological Studies

The applicant has submitted a number of references regarding toxicity data of the pharmacological active substance florfenicol.

- Single Dose Toxicity

The acute toxicity of florfenicol is very low, viz. the oral LD_{50} in rats is > 2000 mg/kg bw. The systemic toxicity is also low, viz. the intraperitoneal LD_{50} in rats is close to 2000 mg/kg bw.

- Repeated Dose Toxicity

Studies with repeated doses were conducted in mice (13 weeks), rats (7, 14, 28 days and 13, 52 weeks) and dogs (14, 28 days and 13, 52 weeks). The most prominent sign of subchronic/chronic toxicity in rats was testicular toxicity with decreased testes weights and testicular tubular degeneration/atrophy. Testicular toxicity was also observed in male rats in a 2-generation study. The lowest NOEL in rats was 3 mg/kg/day and was observed in the chronic toxicity study. Other signs of toxicity observed with repeated administrations in rats were: decreased weight gain and food intake, changes in haematologic and clinical chemistry parameters and increased liver weights. In mice, increased liver weights were observed at high doses (400 mg/kg/day) in the 3-month toxicity study. Testicular degeneration/atrophy was seen at 200 mg/kg/day in the 2-year

toxicity study. Hepatotoxicity (increased liver weights, cellular changes in the gall bladder) was the most prominent sign of toxicity in Beagle dogs. The dog was the most sensitive species and the NOEL was 1 mg/kg bw/day."

- Reproductive Toxicity, including Teratogenicity:

The applicant has submitted references of investigations on reproduction. The results of a multi-generation study and of a 52 week study in rats revealed that florfenicol had adverse effects on the male reproductive system.
Several teratogenic studies were performed in mice (0, 1, 3, 60 mg/kg bw/day) and in rats (0, 4, 12, 40 mg/kg bw/day). High doses induced maternal effects and delayed ossification. The NOELs for maternal toxicity were 3 mg/kg bw/day for mice and 4 mg/kg bw/day for rats. Florfenicol induced no foetal malformation at any dose level and showed no potential for embryo- or fetotoxicity.

- Mutagenicity

The genotoxic properties of florfenicol have been studied by eight *in vitro* and *in vivo* tests. The in vitro CHO Chromosomal Aberration Assay showed an increase of chromosome aberrations at the highest dose (2500 µg/ml) and an increase of endo-reduplication at 1250 and 2500 µg/ml in the presence of rat liver S9 fraction.. As in vitro tests for gene mutation in mouse lymphoma cells and the DNA repair test with primary rat hepatocytes were negative, and since *in vivo* studies (micronuclei and chromosome aberrations) were also negative, florfenicol is considered to be non genotoxic.

Other Studies

The applicant has provided bibliographical data which show that in contrast to chloramphenicol, florfenicol lacks the nitro group located on the aromatic ring that has been associated with chloramphenicol induced non-dose-related irreversible aplastic anemia in men.

Observations in Humans

As florfenicol is exclusively used in animals, no data are available from its use in man.

Microbiological Studies

The applicant made reference to the MRL Summary Report (EMEA, 1994). The bacterial population was comprised of 10 isolates of each of 10 genera/species representative of the human gut flora. The most sensitive microorganism was *Fusobacterium spp.* and its MIC (0.36 µg/ml) was used for establishment of a microbiological ADI.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline in the original dossier for authorization in cattle. In the extension dossier for pigs, justification for referring to the original user safety assessment was given. The product will be used by professionals, i.e. the veterinarian or by the farmer/animal holder under supervision of the veterinarian. The routes of exposure can be dermal: by spilling onto the skin, ocular: by accidental flushing into the eyes or by rubbing the eyes with contaminated hands or clothing, parenteral: by accidental self-injection, oral: by ingestion. There is no specific concern with regard to the systemic effects of florfenicol or one or more of the excipients. The risk characterisation predicts no unacceptably high risk for the unprotected professional user. Warnings and precautions as listed on the product literature are the same with use in cattle and pigs and are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in the original dossier for authorization in cattle and in the extension dossier for pigs. Both ERAs were in compliance with the relevant guideline and showed that no further assessment is required. The assessment concluded that the predicted environmental concentration of florfenicol in soil is below the action limit of 100 µg/kg with use in both target species. No warnings to ensure safety to the environment are therefore required when the product is used as directed.

III.B Residues documentation

Residue Studies

Cattle: The applicant provided a GLP residue depletion study. In this cattle were treated with florfenicol 30% suspension at the recommended single dose of 30 mg florfenicol/kg body weight intramuscular. Samples of liver, fat, kidney, muscle and injection site (core and surroundings) were taken at day 9, 18, 27, 36 and 45 after treatment. The results of the analysis of the tissue samples showed that 36 days after treatment no tissue sample contained residues of florfenicol higher than the MRLs.

Pigs: The applicant provided a GLP residue depletion study for the target species “Pig”. Animals were treated at one single dose of 30 mg florfenicol per kg body weight intramuscular. Samples of liver, skin + fat, kidney, muscle and injection site (core and surroundings) were taken at day 5, 10, 15 and 29 after treatment. The results of the analysis of the tissue samples showed that 20 days after treatment no tissue sample contained residues of florfenicol higher than the MRLs.

The analytical method in both studies was a LC-MS/MS-method. Residue concentrations were measured as the sum of florfenicol and its metabolites and as florfenicol amine. The method was fully validated.

MRLs

Florfenicol is a wide spectrum, synthetic antibacterial and is included in Table 1 of the Annex to Commission Regulation (EC) 37/2010 with the following MRLs for cattle and pigs:

Pharmacologically active substance	Marker residue	Species	MRLs	Target tissues	Other provisions
Florfenicol	Sum of florfenicol and its metabolites measured as florfenicol amine	Bovine	3000 µg/kg 300 µg/kg 200 µg/kg	Liver Kidney Muscle	Not for use in animals producing milk for human consumption
		Porcine	2000 µg/kg 500 µg/kg 300 µg/kg 500 µg/kg	Liver Kidney Muscle Skin + fat	

Withdrawal Periods

Based on the data provided in the GLP studies, the following withdrawal periods were set:

Withdrawal Periods:

Cattle:
Meat and offal: 37 days.
Milk: Do not use in cattle producing milk for human consumption.

Pigs:
Meat and offal: 22 days.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a hybrid application according to Article 13 (3), in which, when applicable, reference is made to “Nuflor injectable solution 300 mg/ml” in the original dossier for authorization in cattle and to “Nuflor Swine Injectable solution 300 mg/ml” in the extension dossier for pigs. The product differs from the reference veterinary medicinal products through its pharmaceutical form but also through a different posology.

Both, the initial application in cattle and the extension application in pigs rely in part on the results of the appropriate safety, pre-clinical and clinical studies on Nuflor® and in part on bridging experimental data for Florgane® to account for the differences between the candidate VMP and the Nuflor® reference products.

With respect to part IV.1 (Pre-clinical studies) reference is made to the dossier of the reference products (RVMPs) for florfenicol-related information rather than product-related information such as pharmacodynamic studies and studies on serum protein binding, distribution, metabolism and excretion of florfenicol.

In addition, proprietary studies on these subjects were provided concerning Pharmacokinetics and Resistance (part IV A). Two studies were provided on MICs for bovine and porcine target pathogens, five studies on pharmacokinetics in cattle and three studies on pharmacokinetics in pigs.

As regards proof of efficacy, bioequivalence with the RVMPs has not been demonstrated. Therefore, efficacy studies in target species are required and were provided (parts IV.B), in which the RVMP served as positive control product. In addition, one dose-titration study in calves with induced *Mannheimia haemolytica* infection and one dose-titration study in pigs with induced *Actinobacillus pleuropneumoniae* infection were provided.

As regards systemic target animal tolerance reference is made to the RVMPs. In cattle, injection site tolerance was examined and documented within the framework of two proprietary residue studies (part III.B). In pigs, injection site tolerance was evaluated in the residue study and in a GMP local tolerance study. In addition, systemic and local tolerance was examined within the framework of pharmacokinetic studies and clinical studies in both target species.

IV.A Pre-Clinical Studies)

Pharmacology

Cattle:

The applicant has conducted 2 MIC studies and provided recent bibliographical data to show that the susceptibility of target pathogens against florfenicol is still deemed to be good and the percentage of resistant strains is low. MIC data are indicated in the SPC.

Pigs:

Two proprietary studies on MICs of porcine target respiratory pathogens as well as relevant literature data on pharmacodynamics of florfenicol (not product-related data) in porcine respiratory pathogens were provided. The susceptibility

of the target pathogens against florfenicol isolated is good. Proprietary MIC data for SRD pathogens are very consistent compared to MIC data found in literature. MIC data are indicated in the SPC.

Pharmacokinetics

Cattle:

The applicant has conducted five studies, one of which was pivotal. It compares the pharmacokinetic behaviour of florfenicol after administration of the RVMP and Florgane 300 mg/ml Suspension for Injection. According to that study in calves, Florgane administered 1X i.m. at 30 mg florfenicol/kg bw and the reference product administered 1 X at 40 mg florfenicol /kg bw s.c. were bioequivalent as regards AUCs, but not bioequivalent as regards T_{max} and C_{max}. Administration of Florgane at 30 mg florfenicol/kg bw i.m. resulted in lower C_{max} and later T_{max} compared with RVMP administered at 40 mg florfenicol/kg bw s.c.. Plasma concentrations above 1 µg/ml were maintained with one single intramuscular injection of 30 mg/kg body weight for on the average 52 hours. Comparison of bioavailability of the same dose of florfenicol after i.m. administration of Florgane and s.c. administration of the reference product reveals that florfenicol from Florgane administered i.m. is more bioavailable than from the reference product administered s.c.

Pigs:

The applicant has conducted three studies.
Plasma florfenicol concentration-time profiles of Florgane 300 mg/ml Susp. for Inj. are demonstrated in a pharmacokinetic study following different dose regimens, partially executed in comparison to the reference veterinary medicinal product (RVMP) Nuflor Swine Injectable, sol. for inj.. When given at the same dose level of 15 mg florfenicol per kg body weight the plasma florfenicol concentration-time profile following i.m. administration of Florgane differs from that of the RVMP by a slower absorption from the injection site with lower initial florfenicol plasma concentrations, a slower elimination from plasma, and a longer persistence of plasma concentrations of > 0.5 µg/ml. According to another pharmacokinetic study, plasma concentrations above 1 µg/ml are maintained with one single intramuscular injection of 30mg/kg body weight for on the average 39 hours. According to the pivotal pharmacokinetic study comparing pharmacokinetics of florfenicol in pigs after i.m. administration of Florgane at 1 x 22.5 mg florfenicol/kg bw and 1 x 30 mg florfenicol/kg bw, resp., and Nuflor ad us vet. at 2 x 15 mg florfenicolkg bw with a 48 h interval, plasma florfenicol concentrations ≥ 1 µg/ml are maintained with one single intramuscular injection of Florgane at 22.5 mg/kg/30mg/kg body weight for 36 ± 8.7/41.2 ± 12.2 hours. After administration of Nuflor plasma florfenicol concentrations ≥ 1 µg/ml are maintained for 11.3±8.1 hours after 1st injection and 14.2 ± 6.9 hours after 2nd

injection. Florfenicol related data on distribution, metabolism and excretion were cited from the RVMP. The product literature adequately reflects the pharmacokinetic findings.

PK/PD analysis

Cattle:

The Applicant provided two PK/PD approaches, both using the T>MIC as most appropriate parameter in order to predict clinical outcomes of florfenicol treatment. The original PK/PD analysis used pharmacokinetic data of Florgane *300 mg/ml Suspension for Injection* and the RVMP generated in different studies while the subsequent analysis compared pharmacokinetic data coming from one and the same study. For reasons of comparability the latter one was considered to be more appropriate and from that was concluded: after administration of Florgane *300 mg/ml Suspension for Injection* (at 30mg/kg b.w.), C_{max} was lower, T_{max} was later and T≥1µg/ml was longer compared to the RVMP. Considering the values for T>MIC_{90} of target pathogens=1µg/ml, results for Florgane *300 mg/ml Suspension for Injection* were more favourable than results for the RVMP. However, since florfenicol possesses bactericidal properties as well, the impact of the different pharmacokinetics (T_{max} and C_{max}) of Florgane *300 mg/ml Suspension for Injection* and the RVMP on clinical efficacy was not predictable. Thus, the outcome of clinical studies was crucial.

Pigs:

Two PK/PD analyses were provided, both using the T>MIC as most appropriate parameter in order to predict clinical outcomes of florfenicol treatment. According to the type of application, i.e. hybrid application, a comparative PK/PD analysis comparing the pharmacokinetics of the RVMP given at the recommended dose of 15 mg/kg bw and Florgane® given at different doses bw was considered reasonable. The initial analysis demonstrated that pharmacokinetic properties of Florgane *300 mg/ml Suspension for Injection* given at the dose of 30mg/kg bw are more favourable than the dose of 15mg/kg bw when compared to the RVMP. An updated PK/PD-analysis based on a further comparative pharmacokinetic study considered Florgane *300 mg/ml Suspension for Injection* at a dose of 22.5 mg/kg bw and compensated for the omission of this dose in the original analysis. PK/PD modelling showed that Florgane *300 mg/ml Suspension for Injection* given at single i.m. doses of 22.5 mg/kg and 30mg/kg bw are more favourable as regards the pivotal PK/PD parameter T≥1µg/ml when compared to the RVMP given i.m. at the recommended treatment regimen of two doses of 15 mg/kg 48 hours apart. Further comparison revealed no significant differences for the parameter AUC/MIC_{90} between each of both doses of Florgane and the RVMP given at the recommended treatment regimen. PK/PD analysis supports the

results with the lower dose of Florgane obtained in the dose-titration study with induced *Actinobacillus pleuropneumoniae* infections and clinical studies.

Tolerance in the Target Species of Animals

Cattle:

Investigations on local tolerance were conducted as part of two residue studies using the recommended dose in the target species. One study used no control, while the other used saline. All doses were administered once by intramuscular route.

Parameters evaluated were by clinical inspection and palpation scoring for swelling, redness, temperature and pain. Injection sites were examined macroscopic and microscopic after slaughter.

Adverse effects consisting of minimal swellings were observed in 25% of treated animals and persisted in one animal at least up to day 13. Inflammatory lesions were found at 6 injection sites (15%) of 4 animals (20%) at day 18.

In the clinical studies, for Florgane *300 mg/ml Suspension for Injection* systemic adverse reactions not worse than for the RVMP were observed. As regards local adverse reactions swellings were observed in 6-11 % of the animals at least until day 21 and pain reactions were found in 4-5% at least until day 5.

Findings on adverse reactions are adequately reflected in the current SPC text proposals.

The product literature accurately reflects the type and incidence of adverse effects which might be expected and considers also findings on adverse reactions which were observed in two clinical studies.

Pigs:

Target animal safety was sufficiently examined in a pivotal study focusing on injection site tolerance. Supporting data do origin from three pharmacokinetic studies, one residue depletion study and two clinical field studies. According to these studies the occurrence of the well known systemic adverse reaction (diarrhoea et cetera) was confirmed and product specific local reactions at the injection sites were identified: intramuscular injection of approximately 5 ml Florgane caused slight or mild swellings at the injection site. Injection site swellings resolved within 6 days in most pigs but may persist up to beyond 12 days. Macroscopic inflammatory lesions at the injection site resolved between 12 and 20 days after administration. Microscopic examination revealed ongoing

healing still at day 28. The product literature reflects adequately the macroscopic injection site and systemic findings.

Resistance

Cattle:

Bibliography and 2 proprietary MIC studies suggest no change in the susceptibility pattern of bovine respiratory *P. multocida, M. haemolytica* and *H. somni* over time. Resistance to target pathogens occurs at very low frequency (from <1 to 3%). Resistance to food-borne pathogens and commensal organisms was reported in varying percentages (0-73%) dependent on the bacterial species and the region of origin were data came from.

Adequate warnings and precautions appear on the product literature.

Pigs:

Bibliography and 2 proprietary MIC studies suggest no change in the susceptibility pattern of porcine respiratory pathogens *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* over time. Resistance of florfenicol in target pathogens is observed in isolated cases, only. Susceptibility of food-born pathogens and commensal organisms is lower and moderate compared to susceptibility of SRD target pathogens. Resistance to florfenicol was reported in low percentages for *S. typhimurium* (4.3%) and *E. coli* (0.7%).

IV.B Clinical Studies

Cattle:

Laboratory Trials

The applicant has conducted a dose titration study investigating an induced *Mannheimia haemolytica* infection in cattle. The study was blinded and placebo controlled. Florgane *300 mg/ml Suspension for Injection* was tested at three different doses, including the recommended dose. The study design was not applicable to draw conclusions on the most appropriate dose. The study was preliminary for dose determination, only.

Field Trials

The applicant has conducted 2 dose confirmation studies. Both studies were blinded and used the same RVMP as control in a non-inferiority design. The studies were conducted according to the same protocol with the restriction that

in one study the RVMP was compared to two different doses of Florgane *300 mg/ml Suspension for Injection*: 30mg/kg and 40mg/kg (multi-site-study, conducted 2008 in Germany and Belgium) while in the second study the RVMP was compared to Florgane *300 mg/ml Suspension for Injection* in the dose of 30mg/kg, only (mono-site study, conducted 2008 in Italy).

90 ruminating bovines were used per group. Only diseased animals showing the inclusion criteria: pyrexia (≥40°C) + abnormal respiratory pattern (score ≥1) + mild or moderate depression (score ≥1) were treated therapeutically. Primary efficacy criterion was treatment success on D7 (rectal temperature <40°C, respiratory pattern ≤1 + depression=0. Co-primary criterion was relapse rate between D8 and 21.

In both studies Florgane *300 mg/ml Suspension for Injection* was equally efficacious and non-inferior to the RVMP in the treatment bovine respiratory disease. When comparing the dosage of 30 mg/kg and 40 mg/kg no superiority of one of those two dosages could be observed.

The recommended dose of Florgane *300 mg/ml Suspension for Injection* at 30mg/kg once intramuscularly was accepted because the higher dose of 40mg/kg is not expected to provide an advantage compared to the lower dose of 30mg/kg. The recommended dose follows the principle: “As low as possible as much as necessary”.

Claims for Indication: The study design of the clinical field studies allowed for assessment of the therapeutic treatment claim, only. However, from a preclinical, clinical and practical point of view no reasons stand against expecting a less favourable outcome as regards a preventive treatment. Thus, studies confirming the preventive claim were not considered necessary.

Pigs:

Laboratory Trials

A dose-finding study using *A. pleuropneumoniae* with a MIC of 0.5µg/ml was provided. According to that study doses of 22.5 mg FF/kg bw and 30 mg FF/kg bw seem to be more effective than doses of 7.5 mg FF/kg bw and 15 mg FF/kg bw. If so, applying the principle of the lowest efficacious dose, a dose of 22.5 mg/kg bw once i.m. was the preferred treatment dose.

Considering that *P. multocida* has a MIC_{90} of 0.5 µg/ml, in principle the study with *A. pleuropneumoniae* is considered enough.

Field Trials

The applicant has conducted 2 dose confirmation studies. Both studies were blinded and used Nuflor containing 300 mg florfenicol/ml (Schering-Plough) as reference veterinary medicinal product (RVMP) in a non-inferiority design. The studies were conducted according to comparable protocols. However, in one study the RVMP was compared to two different doses of Florgane: 22.5 mg/kg and 30 mg/kg (multi-site-study, conducted in 2009 in Germany and Italy), and in the other study the RVMP was compared to Florgane at a dose of 30 mg/kg, only (two-sites study, conducted in 2011 in the Netherlands).

Enrolled pigs of various breeds showing pyrexia (≥ 40.0°C) + abnormal respiratory pattern (score ≥1) + mild or moderate depression (score 1 or 2) were treated with Florgane (German/Italian study at two different single intramuscular doses, i.e. 22.5 mg/kg bw vs. 30 mg/kg bw; Dutch study at 30 mg/kg bw intramuscularly) and Nuflor at its recommended treatment dose of 2 X 15 mg/kg bw intramuscularly 48 hours apart.

Pathological and bacteriological results confirmed an acute infection with *A. pleuropneumoniae* and *P. multocida*.

As primary efficacy criterion served “cure rate” defined as animals not being excluded from the study until day 7 due to swine respiratory disease (SRD), i.e. pigs were defined as cured when having a rectal temperature ≤ 39.9 ° C + respiratory score = 0 + depression score = 0. Animals being withdrawn from the study due to SRD, and animals that needed additional treatment or died due to SRD before or on day 7 were defined as treatment failures. Relapse rate served as co-primary criterion and was defined as number of animals declared cured on day 7 but being withdrawn between day 8 and day 21±1 because of fulfilling the post-inclusion removal criteria (≥ 40.0°C + respiratory pattern score of ≥ 1 or depression score of ≥ 1) or animals necessitating additional treatment of SRD or dying due to SRD. Sum of clinical scores (sum or respiratory and depression score), rectal temperature, respiratory pattern score, depression score and daily body weight gain served as secondary criteria.

In both studies Florgane proved to be equally efficacious and non-inferior to the RVMP in the treatment swine respiratory disease. When comparing the dosage of 30 mg/kg and 22.5 mg/kg no superiority of one of those two dosages over each other could be observed

Taking into account the PK/PD-analysis according to which 22.5 mg/kg bw and 30 mg/kg bw could be efficacious doses and applying the principle of the lowest efficacious dose, a dose of 22.5 mg/kg bw once i.m. was considered the recommended treatment dose.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Safety/efficacy changes

Summary of change **(Type; application number)**	**Section updated in Module 3**	**Approval date**
Addition of target species - pigs (DE/V/0132/001/DX/001)	<IIIA> <IIIB> <IV>	5 June 2012