IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

NUFLOR 300 mg/ml solution for injection for cattle and sheep

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0269/001/DC
Name, strength and pharmaceutical form	NUFLOR 300 mg/ml solution for injection for cattle and sheep
Active substance(s)	Florfenicol
Marketing Authorisation Holder	Intervet Ireland Limited Magna Drive Magna Business Park Dublin 24 Ireland
Legal Basis of application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended. The present application is presented as a line extension (addition of a food-producing target species, sheep) of the existing authorisation for Nuflor Cattle Injectable (florfenicol 300 mg/ml).
Date of Authorisation	20th September 2011
Target species	Cattle and sheep
Indication for use	Cattle: Diseases caused by florfenicol susceptible bacteria. Preventive and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before preventive treatment. Sheep: Treatment of ovine respiratory tract infections due to *Mannheimia haemolytica* and *Pasteurellamultocida* susceptible to florfenicol.

ATCvet code	QJ01BA90
Concerned Member States	BE, DE, DK, EL, ES, FR, IT, LU, NL, PT & UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 benefit/risk analysis is in favour of granting a marketing authorisation.

Note: This assessment report was generated following the assessment of an application for a line extension (addition of a food-producing target species, sheep) of the existing authorisation for Nuflor Cattle Injectable (florfenicol 300 mg/ml). Therefore, data relevant to the new target species only (sheep) are addressed in this report.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains florfenicol 300 mg and the excipients N-methyl-2-pyrrolidone, propylene glycol and macrogol 300.
The container/closure system consists of a colourless Type I glass vial closed with a bromobutyl rubber stopper with aluminium seal.
The choice of formulation is 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 at a licensed manufacturing site.
Process validation data have been presented in accordance with the relevant European guidelines.

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 its specification have been provided.

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

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D.Control on Intermediate Products

Not applicable.

E.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 site have been provided demonstrating compliance with the specification.

F.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.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The present application is presented as a line extension (addition of a food-producing target species, sheep) of the existing authorisation for Nuflor Cattle Injectable (florfenicol 300 mg/ml). Therefore, data relevant to the new target species only (sheep) are addressed in this report.

III.A Safety Testing

Data relating to pharmacodynamics, pharmacokinetics and toxicity of florfenicol have been previously reviewed by the CVMP when presented in support of the original florfenicol MRL application (cattle) and subsequent extensions (to pigs, fish, chicken). Based on those data, florfenicol has been included in Annex 1 of Council Regulation 2377/90 indicating that the active substance has been approved for use in food-producing species. See European Public MRL Assessment Reports for florfenicol. Additional information relating to pharmacodynamics, pharmacokinetics and toxicity of the product in the target species are included in Part IV of the dossier.

A user risk assessment was not provided with the application dossier. However, for the existing cattle and pig products, the following user safety statements have been agreed: '*Care should be taken to avoid accidental self-injection.*
Do not use the product in known cases of sensitivity to propylene glycol and polyethylene glycols.'
Given that 1) the inherent toxicity of the product is identical to that of the existing cattle and pig products, and 2) use of the product in sheep will not result in greater user exposure compared to use in either cattle or pigs, it follows that that same user warnings as agreed for the cattle and pig products should be applied to the sheep product.

Given that the product in question is an injectable antibiotic for the treatment of respiratory disease in sheep, the consideration of potential risk to the environment can, in accordance with current guidance, stop at Phase I: It can be assumed that the product under normal conditions of use will not result in significant environmental exposure and, consequently, will not pose an unacceptable risk to the environment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the user and the environment when the product is used as directed.

III.B Residues Documentation Residue Studies

A GLP confirmatory residue depletion study was conducted in the target species. The florfenicol-derived residues, measured as florfenicol-amine, were below the MRL in all individual animal samples of liver, kidney, non-injection site muscle and injection site muscle by 20, 20, 10 and 30 days after last injection, respectively.

Florfenacol-amine was determined using a HPLC-UV method. The validation data presented confirm that the method is satisfactory for the accurate determination of florfenicol amine residues in sheep tissues.

MRLs

Florfenicol is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Florfenicol	Sum of florfenicol and its metabolites measured as florfenicol-amine	Bovine, ovine, caprine	200 micrograms/kg 3 000 micrograms/kg 300 micrograms/kg	Muscle Liver Kidney	Not for animals from which milk is produced for human consumption. Not for animals from which eggs are produced for human consumption.
		Porcine	300 micrograms/kg 500 micrograms/kg 2 000 micrograms/kg 500 micrograms/kg	Muscle Skin and fat Liver Kidney	
		Poultry	100 micrograms/kg 200 micrograms/kg 2 500 micrograms/kg 750 micrograms/kg	Muscle Skin and fat Liver Kidney	
		Fin fish	1 000 micrograms/kg	Muscle and skin in natural proportions	
		All other food producing species	100 micrograms/kg 200 micrograms/kg 2 000 micrograms/kg	Muscle Fat Liver Kidney	
			300 micrograms/kg		

Withdrawal Periods

A withdrawal period of 39 days was derived based on the injection site data. This corresponds to the withdrawal period that would be determined using the 'alternative' approach based on time residue in individual samples decreases below the MRL plus an addition safety span: in this case, 30 days + 9 days (safety span of 30%). The proposed withdrawal period is ~2 times the statistically determined withdrawal period for liver and kidney and ~4 times the withdrawal period for non-injection site muscle.

Given that florfenicol does not have an MRL for milk, Nuflor Injectable should not be administered to sheep producing milk for human consumption.

IV. CLINICAL ASSESSMENT

The present application is presented as a line extension (addition of a food-producing target species, sheep) of the existing authorisation for Nuflor Cattle Injectable (florfenicol 300 mg/ml). Therefore, data relevant to the new target species only (sheep) are addressed in this report.

IV.APre-Clinical Studies

Tolerance in the Target Species of Animals

The test product is well tolerated when administered to sheep at a dose of 20 mg/kg bodyweight, once daily for three days. The principal adverse effect attributed to treatment is a reduction in food consumption, with consequential effects for weight gain. While a reduction in food consumption at the recommended treatment dose for three days was not reported in any of the target animal safety studies, it is noted that in the clinical field study Nuflor treated animals had a lower weight gain than animals treated with the reference product: this effect was considered possibly related to treatment-related reduced food consumption (food consumption was not measured during this study). Consequently, it is appropriate that the following statements be included in section 4.6 of the SPC:

'A decrease in food consumption may occur during the treatment period. The treated animals recover quickly and completely upon termination of treatment.'

There is no evidence to suggest that the test product is associated with significant injection site reaction. In the clinical field study, only one animal from the Nuflor group was observed with an injection site reaction. This reaction was reported to have resolved in two days. In all other studies, there are no reports of injection site reaction as adverse effects. However, although not evident clinically, evidence of inflammation at the injection site was noted at necropsy in a number of studies. Typically these reactions were mild and, where detected, were resolving (21-28 days after treatment). In view of this, it is considered appropriate that the following statement be included in section 4.6 of the SPC:

'Administration of the product by the intramuscular route may cause inflammatory lesions at the injection site. Typically, these are mild and transient.'

Given that the results of the pivotal target animal safety study provides clear evidence that adverse effects (sometimes severe) are observed if the recommended dose or duration of treatment are increased, section 4.4 of the SPC include a clear statement that the recommended treatment dose or duration of treatment should not be exceeded.

Resistance

Available data relating to antimicrobial resistance for the proposed use of Nuflor for the treatment of ovine respiratory disease provide considerable evidence that such use would present negligible risk of an adverse impact on human or animal health.

Clinical Studies Laboratory Trials

PK/PD data

The applicant has provided detailed pharmacodynamic and pharmacokinetic data to justify the proposed dose for the claimed indication.

·The MIC_{90} values of florfenicol are in the range 0.5 – 1 mg/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:

oflorfenicol 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 micrograms/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 micrograms/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, oafter only two hours exposure, florfenicol exhibits a post-antibiotic effect (ranging from 1 – 3 hours at concentrations >1 microgram/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 micrograms/ml by approximately 1 hour after treatment. Elimination half-life was estimated to be 13.76 + 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 microgram/ml (MIC90) 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. It is 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 microgram/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.)

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 *Mannheimia 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 *Mannheimia 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*.

Dose confirmation studies

Dose confirmation studies were not conducted.

Field Trials

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

It can be 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*. Section 4.9 of the Summary of Product Characteristics includes text clarifying that the recommended treatment dose and treatment interval for sheep is selected based on the time mean florfenicol concentrations are maintained above MIC_{90}.

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 benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

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.

Changes:
None.