IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Norfenicol 300 mg/ml Solution for Injection for Cattle and Pigs

"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/0282/001/DC
Name, strength and pharmaceutical form	Norfenicol 300 mg/ml Solution for Injection for Cattle and Swine
Active substance(s)	Florfenicol
Applicant	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	25th January 2012
Target species	Cattle, Swine
Indication for use	Cattle: Treatment of respiratory tract infections in clinically diseased cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*, susceptible to florfenicol Swine: Treatment of acute outbreaks of respiratory disease caused by strains of *Actinobacillus* *pleuropneumoniae* and *Pasteurella multocida* susceptible to Florfenicol.
ATC vet code	QJ01BA90
Concerned Member States	AT, BE, CZ, DE, DK, EL, ES, HU, IT, LU, NL, PL, RO, SE, SI, SK, 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.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains florfenicol 300 mg and the excipients glycerol formal and pyrrolidone.
The product is marketed in 50 ml, 100 ml, 250 ml and 500 ml type I glass vials and in 50, 100, 250 and 500 ml HDPE plastic vials sealed with bromobutyl bungs and aluminium seals.
50 ml clear type I glass vials as well as the 50 ml, 100ml, 250 ml and 500 ml HDPE plastic vials are presented in a cardboard box.

100 ml, 250 ml and 500 ml glass vials are accompanied by a protective sleeve.

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 on the product 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 this specification have been provided.

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.

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 has been provided.
Batch analytical data from the proposed production sites(s) has been provided demonstrating compliance with the specification.

F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product

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)

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Pharmacological Studies

The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The reference product for this procedure was Nuflor 300 mg/ml Injectable Solution.

The applicant conducted studies to investigate bioequivalence of the test and reference products in each of the target species and for each route of administration. Based on the data presented, bioequivalence was accepted.

As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, results of pharmacological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety

The applicant provided a user safety assessment which showed that when used in accordance with label recommendations, the product will not pose any greater risk to the user than the risks associated with use of the reference product, Nuflor 300 mg/ml Injectable Solution.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users.

Environmental Risk Assessment

The applicant provided a phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. No warnings are therefore required.

III.B Residues Documentation

Residue Studies

GLP residue depletion studies using the final formulation were conducted in cattle and pigs.Samples of tissues were taken from animals at several time points (4 animals per time point) following administration of the product in accordance with the recommended dosing regimen. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period.

The analytical method was HPLC with UV detection. The method was fully validated.

MRLs

Florfenicol is listed in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010 (O.J. 20.1.2010, L15/32).The marker substance is the sum of florfenicol and its metabolites measured as florfenicol amine.
MRLs are listed below:

	Bovine	Porcine
Muscle	200 µg/kg	300 µg/kg
Liver	3000 µg/kg	2000 µg/kg
Kidney	3000 µg/kg	500 µg/kg

Fat/ skin	-	500 µg/kg

Not for use in animals producing milk for human consumption.

Withdrawal Periods

Based on the residue depletion data provided, withdrawal periods of 39 days for meat in cattle when administered twice by intramuscular injection at 20 mg/kg bodyweight and 44 days when administered once by subcutaneous injection at 40 mg/kg bodyweight are justified.

For swine, a withdrawal period of 22 days for meat when administered twice by intramuscular injection at 15 mg/kg bodyweight is justified.

The product is not permitted for use in lactating animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology
The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The reference product for this procedure was Nuflor 300 mg/ml Injectable Solution.

The applicant conducted studies to investigate bioequivalence of the test and reference products in each of the target species and for each route of administration. All three studies were conducted in accordance with GLP.

- Cattle subcutaneous study: the 90% confidence intervals for the pivotal pharmacokinetic parameters lay within the narrower limits of 80-125%.
- Cattle intramuscular study: the 90% confidence intervals for AUC lie within the narrower limits of 80-125%, with the 90% confidence intervals for C_{max} marginally outside the narrower limits of 80-125%, but well within the wider limits of 70-143%.
- Pig intramuscular study: the 90% confidence intervals for AUC lay within the narrower limits of 80-125%, with the 90% confidence intervals for C_{max} marginally outside the wider limits of 70-143%. It was accepted that although the upper confidence interval for C_{max} was marginally exceeded, the impact on efficacy would be negligible. Recognising the fact that the higher C_{max} observed for the test product may have implications for safety, the applicant investigated both target animal safety (see Part IV) and depletion of residues (see Part IIIB) when the test product was administered by the intramuscular route to pigs.

Based on the data presented, bioequivalence was accepted.

Tolerance in the Target Species of Animals

The applicant conducted two target animal tolerance studies using multiples of the recommended dose in the target species. One investigated the tolerance of the test product in pigs when administered via the intramuscular route and the second investigated tolerance in cattle treated subcutaneously. In both studies, a placebo was used as a control.

Parameters evaluated were biochemical and haematological, with general clinical observations and physiological variables also evaluated.
Adverse effects of diarrhoea and peri-anal erythema/oedema were seen following administration of three times the recommended dose in pigs. In cattle, injection site reactions characterised by swelling and hardness were observed in some animals following the recommended dosage.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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.