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

NUFLOR MINIDOSE

Date: 09 October 2013

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0122/001/DX/004
Name, strength and pharmaceutical form	NUFLOR MINIDOSE, 450 mg/ml Solution for injection
Applicant	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleißheim Germany
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Cattle
Indication for use	Preventive and therapeutic treatment of respiratory tract infections in cattle due to Mannheimia haemolytica, Pasteurella multocida and Histophilus somni susceptible to florfenicol. The presence of the disease in the herd should be confirmed before administering preventive treatment.

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 Extension	July 2008 May 2011
Date product first authorised in the Reference Member State	n.a
Concerned Member States for original procedure	BE; BG, CY; CZ; DE; DK; EL; ES; FI; FR; HU; IE; IS, IT; LU; NL; PT; RO; SE, SI; UK

I. SCIENTIFIC OVERVIEW

Nuflor Minidose is a solution for injection containing florfenicol as active ingredient in a concentration of 450 mg/ml. This product mainly differs from the reference veterinary medicinal product (RVMP) Nuflor through a higher concentration of active substance, but also through the excipients. The concentration of florfenicol in the RVMP is 300 mg/ml.

The quality, safety and efficacy aspects of this product are essentially similar to Nuflor. The initial application for Nuflor was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

II. QUALITY ASPECTS

A. Composition

The product contains Florfenicol 450 mg/ml and N-Methylpyrrolidone and Diethylene glycol monoethyl ether.

The product is filled into clear glass vials of 50, 100 and 250 ml. The bromobutyl rubber stoppers are lubricated with silicon oil and sealed with aluminium caps.

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 in accordance with the European Pharmacopoeia and 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.

An Active Substance Master File (ASMF) has been provided by the manufacturer.

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

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 site have been provided demonstrating compliance with the specification.

G. Stability

Stability studies on the active substance are presented in the open part of the ASMF. 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 day stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at room temperature

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13(3) of Directive 2001/82/EC as amended based on the essential similarity of Nuflor Minidose and the reference product Nuflor, results of pharmacological and toxicological tests are not required.

However, bioequivalence of Nuflor Minidose and the RVMP Nuflor was requested to be proven.

The applicant has made full reference to the SPC of the reference product granted in Germany. However, as this was not completely identical to the SPCs authorised for this product in other concerned member states, efforts have been made during the decentralised procedure to produce a harmonised overall accepted product literature for Nuflor Minidose. Warnings and precautions as listed in the product literature are adequate to ensure safety of Nuflor Minidose to the user.

III.A Safety Testing

Pharmacological Studies

See Part IVA Preclinical studies.

Toxicological Studies

Since the application is made on the basis of essentially similarity to a reference product in accordance with Article 13 (3) of Directive 2001/82/EC as amended, data from toxicological studies are not required.

User Safety

Since the application is made in accordance with Article 13 (3) of Directive 2001/82/EC as amended, a detailed User safety assessment is not required. However, the applicant presented some exposure scenarios in compliance with the relevant guideline which shows that the product can be handled safely when the proposed precautions are observed.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The initial assessment concluded that there is concern for the model organisms algae and plants and that the organohalogen might enter groundwater at concentrations higher than 0.1 µg/l. A test on degradation of florfenicol in manure showed that the active transforms into monochloro florfenicol, florfenicol oxamic acid, florfenicol alcohol and florfenicol amine in manure. Taking transformation into account when calculating exposure of the environment to florfenicol, the active is not expected to enter groundwater. Plant toxicity tests with transformation products formed above 10% of the applied amount of florfenicol demonstrated that there is no risk for the environment to be expected from the transformation products based on the

calculation of a cumulative RQ[1] for all relevant compounds (parent and transformation products) at half maximal default manure storage time (46 d).

Residue Studies

Subcutaneous route of administration:
In a GLP study cattle were treated at the maximum recommended dose with 40 mg florfenicol per kg body weight. The dose volume was divided into two equal volumes which were injected on the right and left side of the neck. Groups of animals were slaughtered at 14, 21, 28, 35, 42, 49 and 56 days after treatment. Liver, kidneys, muscle and the left injection site samples were taken.
Highest residue concentrations were found in liver, kidney and in the inner core tissue of injection site (CT) at 14 days after treatment. Only in muscle samples residues were at day 21st after treatment below the MRL of 200 µg/kg. The residues in liver, kidney and CT declined slowly and discontinously up to 42 days after treatment. In general, the residue data show high standard deviations of the individual data at each slaughter time in liver, kidney and CT. The 49th day p.appl. was the first time when all residue concentrations were below the specific MRLs.
A pragmatic approach was used for the determination of a withdrawal period of 64 days after subcutaneous treatment with Nuflor Minidose. This withdrawal period includes the depletion time of 49 days and an additional safety margin of 15 days.

Intramuscular route of administration:

A GLP residue study was provided by the applicant for the intramuscular route of administration with Nuflor Minidose at the maximum recommended dose of 20 mg florfenicol/ kg BW, twice 48 hours apart. All edible tissues including injection site (core tissue and surrounding tissue) were analysed at day 7, 14, 21 and 28 post applicationem. The residue depletion pattern shows a high variability of the individual data at the first three slaughter times especially in injection site tissue.
As requirements of statistical regression analysis were not met, the alternative approach was used for determination of a withdrawal period after intramuscular treatment.
The 28th day post applicationem was the first time when all residue concentrations dropped below their specific MRL. At day 21 in core injection site tissue one residue concentration was reported as 148-fold higher than the muscle MRL (200 µg/ kg) while the other three values are already below MRL. In order to take into account the uncertainties of the residue depletion at injection site a safety margin of 30% of depletion time was considered adequate. Therefore, the alternative approach results in a withdrawal period of 37 days (28 plus 9 days) for the intramuscular route of administration.

[1] risk quotient: the predicted environmental concentration divided by the predicted no effect concentration

Analytical method:
A new HPLC method with fluorescence detection was used for the detection of florfenicol amine in bovine tissue (LOQ = 69 ng florfenicol amine/g). Florfenicol and its metabolites are acid pulped to florfenicol amine and thereafter extracted from the homogenated tissue by liquid/ liquid extraction. The determination of florfenicol amine in the obtained sample extract is performed by HPLC using fluorescence detection. The analytical method was fully validated.

MRLs
Florfenicol is included for use in cattle in the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances in their classification regarding maximum residue limits in foodstuffs of animal origin as follows:

Pharmacologically active substance	Marker residue	Species	MRLs	Target tissue	Other provisions
Florfenicol	Sum of florfenicol and its metabolites measured as florfenicolamine	Bovine	200 µg/kg 3000 µg/kg 300 µg/kg	Muscle Liver Kidney	Not for use in animals from which milk is produced for human consumption.

Both excipients contained in Nuflor Minidose - N-methyl-2-pyrrolidone and diethylene glycol monoethylether - are included in Commission Regulation (EU) No 37/2010 and no MRLs are necessary for these substances.

Withdrawal Periods
Withdrawal periods were established for meat and offal of cattle after treatment with Nuflor Minidose as follows:

Meat and offal:
by subcutaneous injection (at 40 mg/kg bodyweight, once): 64 days
by intramuscular injection (at 20 mg/kg bodyweight, twice): 37 days

Not authorised for use in lactating animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

The efficacy claims for Nuflor Minidose are equivalent to those of the reference veterinary medicinal product (RVMP) Nuflor. As the original application was a generic one according to Article 13(3), pharmacodynamic data and efficacy studies were not required. However, bioequivalence of Nuflor Minidose and the RVMP Nuflor was requested to be proven.

Bioequivalence of Nuflor Minidose and the RVMP Nuflor was proven after single subcutaneous administration at 40 mg/kg body weight. However, bioequivalence of both products was not proven at 20 mg/kg body weight administered intramuscularly twice 48 hours apart.

Thus, an extension application was submitted updating pharmacodynamic data and presenting a clinical efficacy study to permit the use of Nuflor Minidose also by the intramuscular route.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Information was provided to show that the susceptibility and resistance situation of Nuflor Minidose is not expected to be any different from that of Nuflor. The MIC_{90} for *M. haemolytica* against florfenicol ranged between 1.0 µg/ml and 2.0 µg/ml, for *Histophilus somni* between 0.25 µg/ml and 0.5 µg/ml and was 0.5 µg/ml for *P. multocida*. The susceptibility situation of the claimed target pathogens is consistent and comparable for the American and the European region and remained stable since the introduction of florfenicol to the market from 1994 up to now.

The new data presented with the extension application are in line with those provided before.

Pharmacokinetics

The Applicant provided two studies on pharmacokinetics to demonstrate the bioequivalence of Nuflor Minidose and the RVMP Nuflor:

1. Investigation into the bioequivalence of a Nuflor Miniodse and the RVMP Nuflor in cattle after subcutaneous administration of a dose of 40 mg florfenicol/kg bodyweight:

The comparative pharmacokinetic study was GLP-compliant and was conducted in a 2 period, two treatment, two sequence cross over design comprising 20 cattle 7-14 month of age. By statistical analysis of the pharmacokinetic variables C_{max} and $AUC_{(0\text{-}LOQ)}$ bioequivalence of test and the RVMP Nuflor was demonstrated, i.e. the confidence limits for C_{max} and $AUC_{(0\text{-}LOQ)}$ were well within the acceptance limits of 80% - 125%.

From the study results it was concluded that bioequivalence of Nuflor Minidose and Nuflor was demonstrated after subcutaneous administration.

2. Investigation into the bioequivalence of Nuflor Minidose and the RVMP Nuflor on the basis of plasma kinetics in cattle after intramuscular administration of a dose of 20 mg florfenicol/kg bodyweight:

According to that study bioequivalence of both products after intramuscular administration was not shown.

Tolerance in the Target Species of Animals

General and local tolerances were investigated as part of the bioequivalence and residue studies after administration of the test product. Furthermore, systemic and local tolerance after intramuscular administration was investigated during the field efficacy study provided with the extension application

General tolerance:

Waiving of detailed examination of general tolerance was accepted, since general tolerance of florfenicol is well known and the excipients are deemed unproblematic as regards systemic tolerance. In the studies systemic adverse reactions known after administration of florfenicol were monitored. In the product literature the adverse reactions regarding general tolerance are mentioned in accordance with the wording of the reference product Nuflor.

Local tolerance:

Subcutaneous administration:

Data on local tolerance at the injection sites after subcutaneous administration of injection volumes < 10 ml per injection site were collected within the framework of the bioequivalence studies.

After administration transient local algesia for some days and persistence of local reactions which were still observable in a considerable number of animals at day 61 after injection were monitored.

From this study it is concluded that clinically obvious swelling at the injection site after subcutaneous injection can be expected to persist for at least 61 days post injectionem in the majority of animals.

Further, local tolerance at the injection sites after subcutaneous administration was examined within the framework of the residue study.

In this study injection volumes ranged between 10.5 and 11.5 ml per site. Two days after subcutaneous injection almost all animals had developed painful swelling of remarkable volumes with increased temperature. Pain and increased temperature was obvious at least for 2 days post injectionem. At the end of the observation period, at day 42 after treatment hard swellings were still present in 50% of the

animals. In general, the macroscopic pathological findings revealed greater sizes of the alterations than documented in the in vivo examinations.

It is concluded that studies examining local tolerance at the injection sites after subcutaneous administration revealed clinically obvious swellings at the injection sites. Post-mortem examinations of the injection sites revealed that inflammation, degeneration and necrosis may persist at least for 42 days after administration. According to the bioequivalence study swelling at the injection site was detected until 61 days after injection. The SPC reflects the findings after subcutaneous administration adequately under section “4.6 Adverse reactions”.

Intramuscular administration:

In a pharmacokinetic study diffuse swelling after intramuscular administration of Nuflor Minidose at 20 mg/kg body weight was found up to day 7. At the next examination of the injection sites on day 14 no swellings were detectable. This means, according to these findings clinically obvious swelling at the injection site after intramuscular injection of Nuflor Minidose can be expected to resolve within 14 days post injectionem.

The study examining local tolerance at the injection sites after intramuscular administration of Nuflor Minidose at therapeutic doses and maximum injection volumes of 10 ml per injection site resulted in clinically obvious swellings up to 24 days, and in pathologically detectable inflammatory lesions at the injection site, which may persist 37 days after injection.

The systemic and local tolerance results of the clinical field study (see below) are favourable compared with those of the tolerance study.

The product literature does adequately address the findings of the tolerance study.

Resistance

Information was provided to show that the susceptibility and resistance situation of florfenicol remained stable since its introduction to the market from 1994 up to now.

According to literature evaluated in the context of the extension application two cases of a resistant *P. multocida* have been described. Resistance gene was located on a plasmid and would therefore most likely be transmissible by horizontal transfer of plasmids. However, at present the potential for development of resistance is regarded as low. Relevant information on pharmacodynamic properties including information on mechanism and state of resistance is addressed in the SPC.
Co-resistance has been identified in the food-borne pathogen Salmonella typhimurium. Co-resistance has been identified, too, in E.coli (respiratory and

digestive) in bovine in France. This is addressed in the product literature mentioning – in addition – that this has not been observed in the target pathogens.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

Studies were not presented.

Field Trials

Studies on evaluation of the field efficacy and safety of Nuflor Minidose when administered subcutanously for the treatment of bovine respiratory disease (BRD) were not provided since bioequivalence with the RVMP Nuflor has been demonstrated.

However, bioequivalence of Nuflor Minidose and the RVMP Nufor was not demonstrated after intramuscular administration. Thus, a controlled, multi-centered, randomized, investigator-blinded study to evaluate the field efficacy and safety of Nuflor Minidose when administed intramuscularly in comparison to Nuflor for the treatment of bovine respiratory disease was provided with the extension application.

In this study cattle showing clinical signs of BRD (elevated rectal temperature and abnormal respiratory signs and depression) were enrolled and randomly allocated to two treatment groups treated intramuscularly either with Nuflor Minidose or Nuflor at 20 mg/kg body weight twice 48 hours apart. At study start and when animals were classified as treatment failures a nasopharyngeal swab was taken and samples were examined for *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*. Florfenicol MICs were determined. Animals were observed for 14 days after initiation of treatment. The pivotal criterion of efficacy was non-inferiority of Nuflor Minidose to Nuflor at a margin of 20 percent (confidence level 90%) with regard to the cumulative rate of failures on day 14 after 2nd injection. Secondary parameters were total cure after 14 days, and intermediate failure rate after 5 days. Furthermore, changes throughout the study in rectal temperature, depression and respiratory scores were compared between groups. Adverse events, injection site reactions, and bacteriological results were tabulated. The efficacy and safety of Nuflor Minidose in the treatment of cattle diagnosed with acute bovine respiratory disease was demonstrated in this field study. Nuflor Minidose was not inferior to Nuflor. Bacterial results (MIC) are in line with the data presented on pharmacodynamics. Thus, the claimed indication of use authorized for the reference product do apply to the test product as well.

There was no systemic adverse reaction due to florfenicol. In the Nuflor Minidose treated cattle the incidence of injection site reactions reached 3.41% from day 1 to day 3. After day 3, the incidence went down and faded away at day 6. These findings are favorable compared with pre-clinical studies investigating injection site tolerance.

A study to prove the prevention claim was not conducted. However, it is reasonable to omit such study because i) there is no reason to expect that Nuflor Minidose will not be non-inferior to Nuflor in the preventive treatment when having demonstrated being non-inferior in the therapeutic treatment, ii) a number of veterinary medicinal products containing florfenicol are authorized in the EU for treatment and prevention of BRD recommending posologies that apply for treatment as well as for prevention, iii) Nuflor Minidose at 20 mg/kg body weight by two intramuscular injections 48 hours apart provides florfenicol plasma levels that remain above the MIC_{90} of most target respiratory pathogens there is no reason to expect differences for therapeutic or preventive efficacy,

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**
DE/V/0122/001/X/004 • *New route of administration (intramuscular) and new dose regimen*	III, IV	30 May 2011