[Version 8, 10/2012]

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection for cattle

ES: Flomac 450 mg/ml solution for injection for cattle
FI: Nuflor vet Minidose 450 mg/ml solution for injection for cattle
FR: Nuflor 450 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Florfenicol……..450.00 mg

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear colourless to yellow solution for injection

4. CLINICAL PARTICULARS

4.1 Target species

Cattle

4.2 Indications for use, specifying the target species

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.

4.3 Contraindications

Do not use in adult bulls intended for breeding purposes.
Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals:
The product should be used in conjunction with susceptibility testing and take into account official and local antimicrobial policies.
Do not use where resistance to florfenicol or other amphenicols is known to occur.
Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to florfenicol and other amphenicols.
The prolonged or repeated use of the veterinary medicinal product should be avoided by

improving farming management practices, cleaning and disinfection measures and eliminating any stress condition.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Care should be taken to avoid accidental self-injection. In case of self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. Avoid direct contact with skin, mouth and eyes. Wash hands after treatment.

4.6 Adverse reactions (frequency and seriousness)

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

Subcutaneous injection of the product at the maximum recommended volume of 10 mL per injection site may cause transient local algesia and clinically obvious swelling at the injection site. Local algesia may persist for some days. Injection site swellings decrease over time but may persist for up to 61 days.

Intramuscular injection of the product at the maximum recommended volume of 10 mL per injection site may cause transient local algesia and clinically obvious swelling at the injection site. Local algesia may persist for some days. Injection site swellings decrease over time but may persist for up to 24 days. Inflammatory lesions at the injection site (seen at necropsy) may persist for 37 days after injection.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals have not revealed any evidence of embryo- or foetotoxic potential for florfenicol.
However, the effect of florfenicol on bovine reproductive performance and pregnancy has not been assessed. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

SC route: 40 mg/kg body weight (4 ml/45 kg) to be administered once only.
IM route: 20 mg/kg body weight (2 ml/45 kg) to be administered twice 48 hours apart.

The injection should only be given in the neck. The dose volume given at any one injection site should not exceed 10 ml.

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

Swab septum before removing each dose. Use a dry, sterile needle and syringe.
For 250 ml vials, do not broach the vial more than 25 times.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No data available. .

4.11 Withdrawal periods

Meat and offal:
by SC (at 40 mg/kg body weight, once): 64 days
by IM (at 20 mg/kg bodyweight, twice): 37 days

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use
ATCVet code: QJ01BA90

5.1 Pharmacodynamic properties

Florfenicol is a synthetic broad-spectrum antibiotic effective against most Gram-positive and Gram-negative bacteria isolated from domestic animals. Florfenicol acts by inhibiting protein synthesis at the ribosomal level and is bacteriostatic and time-dependent. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in bovine respiratory disease which include *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

Florfenicol is considered to be a bacteriostatic agent, but *in vitro* studies of florfenicol demonstrate bactericidal activity against *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

For *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* the following breakpoints have been determined for florfenicol in bovine respiratory disease: susceptible: ≤2 µg/ml, intermediate: 4 µg/ml, resistant: ≥8 µg/ml.

Resistance to florfenicol is mainly mediated by an efflux system due to specific (flo-R) or multidrug transporters (AcrAB-TolC). The genes corresponding to these mechanisms are coded on mobile genetic elements such as plasmids, transposons or genes cassettes.

Surveillance data of the susceptibility of target field isolates from cattle collected between 1995 and 2009 across Europe show a constant activity of florfenicol with no finding of resistant isolates. In the recent literature, one resistant isolate of *P. multocida* was reported from a calf in Germany in 2007 harbouring a plasmid mediated flo-R. No co-resistance to other antibiotic families was observed. Cross-resistance with chloramphenicol can occur.

Resistance to florfenicol and other antimicrobials has been identified in the food-borne pathogen *Salmonella typhimurium* and co-resistance with the third-generation cephalosporins has been observed in respiratory and digestive *Escherichia Coli.* This has not been observed for the target pathogens.

5.2 Pharmacokinetic particulars

After parenteral application florfenicol is mainly excreted via urine and to a small extent via faeces, mainly as parent compound but also followed by florfenicol amine and florfenicol oxamic acid.
The administration of the product by the subcutaneous route at the recommended dose of 40 mg/kg maintained efficacious plasma levels of florfenicol in cattle above the MIC_{90} of 0.5 µg/ml and 1.0 µg/ml for 90.7 hours and 33.8 hours, respectively. Maximum mean serum concentration (Cmax) of 1.8 µg/ml occurred 7 hours (Tmax) after dosing.
The administration of the product by the intramuscular route at the recommended dose of 20 mg/kg maintained efficacious plasma levels of florfenicol in cattle above the MIC_{90} of

0.5 µg/ml and 1.0 µg/ml for 48.7 hours and 30.3 hours, respectively. Maximum mean serum concentration (Cmax) of 3.0 µg/ml occurred 6 hours (Tmax) after dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-Methylpyrrolidone
Diethylene glycol monoethyl ether

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 28 days

6.4. Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

50, 100 and 250 ml colourless type II glass multiple dose vials, sealed with bromobutyl rubber stoppers secured with aluminium overseal.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands
Tel.: +31 /485 587 600
Fax.: +31 /485 577 333

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>…

10. DATE OF REVISION OF THE TEXT

{MM/YYYY} or <month YYYY>

PROHIBITION OF SALE, SUPPLY AND/OR USE
To be supplied only on veterinary prescription

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton box for the 50-, 100- and 250-mL vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection for cattle
Florfenicol

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Active substance: Florfenicol 450 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 mL
100 mL
250 mL

5. TARGET SPECIES

Cattle

6. INDICATION(S)

Not applicable for the outer package.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Subcutaneous and intramuscular administrations.

8. WITHDRAWAL PERIOD

Meat and offal: by SC (at 40 mg/kg body weight, once): 64 days
by IM (at 20 mg/kg body weight, twice): 37 days

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

9. SPECIAL WARNINGS

Care should be taken to avoid accidental self-injection. Avoid direct contact with skin, mouth and eyes. Wash hands after treatment – Read the package leaflet before use.

10. EXPIRY DATE

<EXP {month/year}>

Shelf life after first opening the container: 28 days

11. SPECIAL STORAGE CONDITIONS

This veterinary medicinal product does not require any special temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused product or waste materials should be disposed of in accordance with national requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally.]

16. MARKETING AUTHORISATION NUMBER(S)

[To be completed in accordance with national requirements after conclusion of the procedure.]

17. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <BN> {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label for the 50-, 100- and 250-mL vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection for cattle
Florfenicol

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Active substance: Florfenicol 450 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 mL
100 mL
250 mL

5. TARGET SPECIES

Cattle

6. INDICATION(S)

Not applicable for the immediate package.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Subcutaneous and intramuscular administrations.

8. WITHDRAWAL PERIOD

Meat and offal: by SC (at 40 mg/kg body weight, once): 64 days
by IM (at 20 mg/kg body weight, twice): 37 days

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

9. SPECIAL WARNINGS

Avoid accidental self-injection. Read the package leaflet before use.

10. EXPIRY DATE

<EXP {month/year}>

<Once broached,/opened, use by…>

Shelf life after first opening container: 28 days

11. SPECIAL STORAGE CONDITIONS

This veterinary medicinal product does not require any special temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused product or waste materials should be disposed of in accordance with national requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally.]

16. MARKETING AUTHORISATION NUMBER(S)

[To be completed in accordance with national requirements after conclusion of the procedure.]

17. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <BN> {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

Nuflor Minidose 450 mg/ml solution for injection for cattle

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
[To be completed nationally.]

Manufacturers for the batch release:
Intervet International GmbH
Feldstrasse 1A
85716 Unterschleissheim
Germany

and

TriRx Segré
La Grindolière
Zone Artisanale
Segré
49500 Segré-en-Anjou Bleu
France

and

Vet Pharma Friesoythe GmbH
Sedelsberger Str. 2-4
26169 Friesoythe
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection for cattle
Florfenicol

ES: Flomac 450 mg/ml solution for injection for cattle
FI: Nuflor vet Minidose 450 mg/ml solution for injection for cattle
FR: Nuflor 450 mg/ml solution for injection for cattle

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Nuflor Minidose is a clear colourless to yellow solution containing 450 mg florfenicol / ml.

4. INDICATIONS

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.

5. CONTRAINDICATIONS

Do not use in adult bulls intended for breeding purposes.
Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

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

Subcutaneous injection of the product at the maximum recommended volume of 10 mL per injection site may cause transient local algesia and clinically obvious swelling at injection site. Local algesia may persist for some days. Injection site swellings decrease over time but may persist for up to 61 days.

Intramuscular injection of the product at the maximum recommended volume of 10 mL per injection site may cause transient local algesia and clinically obvious swelling at the injection site. Local algesia may persist for some days. Injection site swellings decrease over time but may persist for up to 24 days. Inflammatory lesions at the injection site (seen at necropsy) may persist for 37 days after injection.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle

8. DOSAGE FOR EACH SPECIES, ROUTES AND METHOD OF ADMINISTRATION

SC route: 40 mg/kg body weight (4 ml/45 kg) to be administered once only.
IM route: 20 mg/kg body weight (2 ml/45 kg) to be administered twice 48 hours apart.

The injection should only be given in the neck. The dose volume given at any one injection site should not exceed 10 ml.

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

9. ADVICE ON CORRECT ADMINISTRATION

Swab septum before removing each dose. Use a dry, sterile needle and syringe.
For 250 ml vials, do not broach the vial more than 25 times.

10. WITHDRAWAL PERIOD

Meat and offal: by SC (at 40 mg/kg body weight, once): 64 days
by IM (at 20 mg/kg bodyweight, twice): 37 days

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

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Shelf-life after first opening the container: 28 days

12. SPECIAL WARNINGS

Special precautions for use in animals:
The product should be used in conjunction with susceptibility testing and take into account official and local antimicrobial policies.
Do not use where resistance to florfenicol or other amphenicols is known to occur.
Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to florfenicol and other amphenicols.
The prolonged or repeated use of the veterinary medicinal product should be avoided by improving farming management practices, cleaning and disinfection measures and eliminating any stress condition.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Care should be taken to avoid accidental self-injection. In case of self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Avoid direct contact with skin, mouth and eyes. Wash hands after treatment.

Pregnancy:
Studies in laboratory animals have not revealed any evidence of embryo- or foetotoxic potential for florfenicol.
However, the effect of florfenicol on bovine reproductive performance and pregnancy has not been assessed. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.
Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIAL, IF ANY

Medicines should not be disposed of via wastewater or household waste.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

[To be completed in accordance with national requirements after conclusion of the procedure.]

15. OTHER INFORMATION

50, 100 and 250 ml vials.
Not all pack sizes may be marketed.
When the container is opened for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded should be worked out. This discard date should be written in the space provided on the label.