[Version 9,03/2022] corr. 11/2022

ANNEX I

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

1 ml of the solution for injection contains:

Active substances:
Florfenicol 450 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
N-methylpyrrolidone	350 mg
Diethylene glycol monoethyl ether	

Clear, colourless to yellow solution for injection.

3. CLINICAL INFORMATION

3.1 Target species

Cattle.

3.2 Indications for use for each target species

Metaphylactic 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 metaphylactic treatment.

3.3 Contraindications

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

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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.

Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of foetotoxic effects. Women of childbearing age, pregnant women or women suspected of being pregnant should use the veterinary medicinal product with serious caution to avoid accidental self-injection.

The veterinary medicinal product may cause hypersensitivity (allergy) in some people. People with known hypersensitivity to florfenicol should avoid contact with the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle:

Very common (>1 animal / 10 animals treated):	Injection site pain[1,2,3], Injection site swelling[1,4], Injection site inflammation [1,5], Injection site lesion[1,5]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[6]; Soft stool[2,6]

[1] After injection of the product at the maximum recommended volume of 10 mL per injection site
[2] Transient
[3] Lasting for some days
[4] Lasting up to 61 days after subcutaneous and up to 24 days after intramuscular injection
[5] Seen at necropsy and lasting for 37 days after intramuscular injection
[6] Quick and complete recovery upon termination of treatment

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing

authorisation holder <or its local representative> or the national competent authority via the national reporting system. See also section "Contact details" of the package leaflet.
{< > to be adjusted nationally}

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established in cattle during pregnancy, lactation or in animals intended for breeding. Studies in laboratory animals have not revealed any evidence of embryo- or foetotoxic potential for florfenicol. Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of foetotoxic effects.
Use only according to the benefit-risk assessment by the responsible veterinarian.

Fertility:
Do not use in adult bulls intended for breeding (see section 3.3).

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Subcutaneous use: 40 mg/kg body weight (4 ml/45 kg) to be administered once only.
Intramuscular use: 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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No data available.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

To be completed nationally.

3.12 Withdrawal periods

Meat and offal: Subcutaneous use (at 40 mg/kg body weight, once): 64 days.
Intramuscular use (at 20 mg/kg bodyweight, twice): 37 days.

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

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01BA90

4.2 Pharmacodynamics

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.

4.3 Pharmacokinetics

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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 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

5.3 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.

5.4 Nature and composition of immediate packaging

Colourless type II glass multiple dose vials, sealed with bromobutyl rubber stoppers secured with aluminium overseal.

Package sizes:
1 vial of 50 ml in a cardboard box
1 vial of 100 ml in a cardboard box
1 vial of 250 ml in a cardboard box

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater <or household waste>.
< >*To be adjusted nationally*.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B.V.

7. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

8. DATE OF FIRST AUTHORISATION

{DD month YYYY}.

To be completed nationally.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD month YYYY}

To be completed nationally.

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

To be completed nationally.

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON BOX (50, 100 and 250 mL presentations)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

1 mL of the solution for injection contains 450 mg florfenicol and 350 mg N-methylpyrrolidone.

3. PACKAGE SIZE

50 mL
100 mL
250 mL

4. TARGET SPECIES

Cattle.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Subcutaneous and intramuscular use.

7. WITHDRAWAL PERIODS

Meat and offal: Subcutaneous use (at 40 mg/kg body weight, once): 64 days.
Intramuscular use (at 20 mg/kg body weight, twice): 37 days.

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

8. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use within 28 days.

9. SPECIAL STORAGE PRECAUTIONS

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.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

14. MARKETING AUTHORISATION NUMBERS

To be completed nationally.

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL (label for the 100 and 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose 450 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

1 mL of the solution for injection contains 450 mg florfenicol and 350 mg N-methylpyrrolidone.

3. TARGET SPECIES

Cattle.

4. ROUTES OF ADMINISTRATION

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

5. WITHDRAWAL PERIODS

Meat and offal: Subcutaneous use (at 40 mg/kg body weight, once): 64 days.
Intramuscular use (at 20 mg/kg body weight, twice): 37 days.

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

6. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use within 28 days.

7. SPECIAL STORAGE PRECAUTIONS

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.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL (50 ml presentations)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nuflor Minidose

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

450 mg/ml Florfenicol

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use within 28 days.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

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. Composition

The solution for injection contains 450 mg florfenicol and 350 mg N-methylpyrrolidone per ml.
Clear, colourless to yellow solution for injection.

3. Target species

Cattle.

4. Indications for use

Metaphylactic 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 metaphylactic treatment.

5. Contraindications

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

6. Special warnings

Special precautions for safe use in the target species:
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.

Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of foetotoxic effects. Women of childbearing age, pregnant women or women suspected of being

pregnant should use the veterinary medicinal product with serious caution to avoid accidental self-injection.

The veterinary medicinal product may cause hypersensitivity (allergy) in some people. People with hypersensitivity to florfenicol should avoid contact with the veterinary medicinal product.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established in cattle during pregnancy, lactation, lay or in animals intended for breeding. Studies in laboratory animals have not been revealed any evidence of embryo- or foetotoxic potential for florfenicol. Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of foetotoxic effects.
Use only according to the benefit-risk assessment by the responsible veterinarian.

Fertility:
Do not use in adult bulls intended for breeding.

Interaction with other medicinal products and other forms of interaction:

None known.

Overdose:

No information available.

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

7. Adverse events

Cattle

Very common (>1 animal / 10 animals treated):	Injection site pain[1,2,3], Injection site swelling[1,4], Injection site inflammation [1,5], Injection site lesion[1,5]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[6]; Soft stool[2,6]

[1] After injection of the product at the maximum recommended volume of 10 mL per injection site
[2] Transient
[3] Lasting for some days
[4] Lasting up to 61 days after subcutaneous and up to 24 days after intramuscular injection
[5] Seen at necropsy and lasting for 37 days after intramuscular injection
[6] Quick and complete recovery upon termination of treatment

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder <or the local representative of the marketing authorisation holder> using the contact details at the end of this leaflet, or via your national reporting system: <{national system details}.

{<to be adjusted nationally<}

8. Dosage for each species, routes and method of administration

Subcutaneous use: 40 mg/kg body weight (4 ml/45 kg) to be administered once only.
Intramuscular use: 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 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 periods

Meat and offal: Subcutaneous use (at 40 mg/kg body weight, once): 64 days.
Intramuscular use (at 20 mg/kg bodyweight, twice): 37 days.

Not authorised for use in 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 precautions for disposal

Medicines should not be disposed of via wastewater or <household waste>.
< > to be adjusted nationally

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

<Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.>
< > to be adjusted nationally

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Package sizes:
1 vial of 50 ml in a cardboard box
1 vial of 100 ml in a cardboard box
1 vial of 250 ml in a cardboard box
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

DD month YYYY

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder <and manufacturer responsible for batch release> <and contact details to report suspected adverse reactions>:

{<to be adjusted nationally<}

Manufacturer responsible for batch release:

Intervet International GmbH
Feldstrasse 1A
85716 Unterschleissheim
Germany

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

Vet Pharma Friesoythe GmbH
Sedelsberger Strasse 2 – 4
26169 Friesoythe
Germany

<Local representatives <and contact details to report suspected adverse reactions>:>

{< > to be adjusted nationally}

<For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

{< > to be adjusted nationally}