ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Florfenicol 300 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-methyl-2-pyrollidone	250 mg
Propylene glycol	
Macrogol 300	

Clear, light yellow to straw-coloured, somewhat viscous solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle and sheep.

3.2 Indications for use for each target species

Cattle:
Diseases caused by florfenicol susceptible bacteria.
Metaphylactic 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 metaphylactic treatment.

Sheep:
Treatment of ovine respiratory tract infections due to *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to florfenicol.

3.3 Contraindications

Do not use in adult bulls and rams intended for breeding purposes.
Do not use in cases 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 veterinary medicinal product should be used in conjunction with susceptibility testing and take into account official and local antimicrobial policies.
The safety of the product has not been established in sheep younger than 7 weeks of age.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

People with known hypersensitivity to propylene glycol and polyethylene glycols should avoid contact with the veterinary medicinal product. In case of accidental contact with skin or eyes, rinse immediately with plenty of water.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of fetotoxic 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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1]; Loose stool[1]; Injection site inflammation[2], Injection site lesion[2]; Anaphylaxis.

[1] Quick and complete recovery upon termination of treatment.
[2] May persist for 14 days after intramuscular and subcutaneous administration.

Sheep:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1]; Injection site inflammation[2], Injection site lesion[2].

[1] Quick and complete recovery upon termination of treatment.
[2] Mild and may persist up to 28 days after intramuscular administration.

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 the package leaflet for respective contact details.
{< > to be adjusted nationally}

3.7 Use during pregnancy, lactation or lay

Pregnancy, lactation and fertility:
The safety of the veterinary medicinal product has not been established in cattle and sheep during pregnancy, lactation or in animals intended for breeding. Laboratory studies in rabbits and rats with

the excipient N-methyl pyrrolidone have shown evidence of fetotoxic effects. Use only according the benefit-risk-assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

No data available.

3.9 Administration routes and dosage

Swab septum before removing each dose. Use a dry sterile needle and syringe.
To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The vials should not be broached more than 20 times. User should therefore select the most appropriate vial size according to the target species to be treated.
When treating groups of animals at the same time, use of a draw-off needle in the vial stopper is recommended to avoid excess stopper broaching. The draw-off needle should be removed after treatment.

For treatment
Cattle:
Intramuscular use: 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart using a 16 gauge needle.
Subcutaneous use: 40 mg/kg bodyweight (2 ml/15 kg) to be administered once only using a 16 gauge needle. The dose volume given at any one injection site should not exceed 10 ml.
The injection should only be given in the neck.

Sheep:
Intramuscular use: 20 mg florfenicol/kg bodyweight (1 ml/15 kg) to be administered daily for three consecutive days. The volume administered per injection site should not exceed 4 ml.

Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 μg/ml) for up to 18 hours after administration of the veterinary medicinal product at the recommended treatment dose. The pre-clinical data supported the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 μg/ml.

For metaphylaxis
Cattle:
Subcutaneous use: 40 mg/kg bodyweight (2 ml/15 kg) to be administered once only using a 16 gauge needle. The dose volume given at any one injection site should not exceed 10 ml.
The injection should only be given in the neck.

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

Cattle:
No symptoms other than those described in section 3.6.

Sheep:
After administration of 3 times the recommended dose or more, a transient reduction in feed and water consumption has been observed. Additional effects included an increased incidence of lethargy, emaciation and loose faeces.
Head tilt was seen after administration of 5 times the recommended dose and was considered most likely a result of irritation at the injection site.

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

Not applicable.

3.12 Withdrawal periods

Meat and offal
Cattle: IM use (20 mg/kg bodyweight, twice):30 days.
SC use (40 mg/kg bodyweight, once): 44 days.
Sheep: 39 days.

Milk
Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce 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. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in ovine and bovine respiratory disease which include *Mannheimia haemolytica, Pasteurella multocida,* and for cattle *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*.

MIC data for the target pathogens are presented in the table below:

Species	**Range (µg/ml)**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**
Mannheimia haemolytica (n=151)	0.25 - 2	1	1
Pasteurella multocida (n=88)	0.25 - 0.5	0.5	0.5

Strains were isolated from sheep suffering from respiratory tract infection in Germany, United Kingdom, Spain and France between 2006 and 2010.

4.3 Pharmacokinetics

Cattle:
Intramuscular administration at the recommended dose of 20 mg/kg maintains efficacious blood levels in cattle for 48 hours. Maximum mean serum concentration (C_{max}) of 3.37 µg/ml occurs at 3.3 hours (t_{max}) after dosing. The mean serum concentration 24 hours after dosing was 0.77 µg/ml.

Subcutaneous administration at the recommended dose of 40 mg/kg maintains efficacious blood levels in cattle (ie above the MIC_{90} of the main respiratory pathogens) for 63 hours. Maximum serum concentration (C_{max}) of approximately 5 µg/ml occurs approximately 5.3 hours (t_{max}) after dosing. The mean serum concentration 24 hours after dosing is approximately 2 µg/ml.

The harmonic mean elimination half-life was 18.3 hours.

Sheep:
After initial intramuscular administration of florfenicol (20 mg/kg), the mean maximum serum concentration of 10.0 μg/ml is reached after 1 hour. Following the third intramuscular administration, the maximum serum concentration of 11.3 μg/ml is reached after 1.5 hours. The elimination half-life was estimated to be 13.76 + 6.42h. Bioavailability is about 90 %.

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

Do not store above 25 °C.
Do not refrigerate.
Protect from frost.

5.4 Nature and composition of immediate packaging

50, 100 and 250 ml colourless Type I glass vials closed with bromobutyl rubber stoppers with aluminium seals.

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.

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

{To be completed nationally, in accordance with SPOR}

7. MARKETING AUTHORISATION NUMBER(S)

{To be completed nationally}

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

{To be completed nationally}

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

{DD/MM/YYYY}
{To be completed nationally}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

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 for the 50, 100 and 250 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

NUFLOR 300 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Florfenicol 300 mg

3. PACKAGE SIZE

50 ml
100 ml
250 ml

4. TARGET SPECIES

Cattle and sheep.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

For treatment:
Cattle: Intramuscular and subcutaneous use.
Sheep: Intramuscular use.
For metaphylaxis:
Cattle: Subcutaneous use.

7. WITHDRAWAL PERIODS

Withdrawal periods:

Meat and offal

Cattle:	IM use (20 mg/kg bodyweight, twice):	30 days.
	SC use (40 mg/kg bodyweight, once):	44 days.
Sheep:		39 days.

Milk
Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}

Shelf life after first opening the immediate packaging: 28 days.
Once opened, use by…

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.
Do not refrigerate.
Protect from frost.

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, in accordance with SPOR}

14. MARKETING AUTHORISATION NUMBERS

{To be completed nationally}

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Label for the 100 and 250 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

NUFLOR 300 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Florfenicol 300 mg

3. TARGET SPECIES

Cattle and sheep.

4. ROUTES OF ADMINISTRATION

Treatment: Intramuscular and subcutaneous use.
Metaphylaxis: Subcutaneous use.

5. WITHDRAWAL PERIODS

Withdrawal periods:

Meat and offal
Cattle: IM use (20 mg/kg bodyweight, twice):30 days.
SC (40 mg/kg bodyweight, once): 44 days.
Sheep: 39 days.
Milk
Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.

6. EXPIRY DATE

Exp. {mm/yyyy}

Shelf life after first opening the immediate packaging: 28 days.
Once opened, use by…

7. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.
Do not refrigerate.
Protect from frost.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

{To be completed nationally, in accordance with SPOR}

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for the 50 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

NUFLOR 

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Florfenicol 300 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Shelf life after first opening the immediate packaging: 28 days
Once opened, use by…

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

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

2. Composition

Each ml contains:

Active substance:
Florfenicol 300 mg

Excipients:
N-methylpyrrolidone 250 mg

Clear, light yellow to straw-coloured, somewhat viscous solution.

3. Target species

Cattle and sheep.

4. Indications for use

Cattle:
Diseases caused by florfenicol susceptible bacteria.
Metaphylactic 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 metaphylactic treatment.

Sheep:
Treatment of ovine respiratory tract infection due to *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to florfenicol.

5. Contraindications

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

6. Special warnings

None.

Special precautions for safe use in the target species:

The veterinary medicinal product should be used in conjunction with susceptibility testing and take into account official and local antimicrobial policies.
The safety of the veterinary medicinal product has not been established in sheep younger than 7 weeks of age.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

People with known hypersensitivity to propylene glycol and polyethylene glycols should avoid contact with the veterinary medicinal product. In case of accidental contact with skin or eyes, rinse immediately with plenty of water.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of fetotoxic 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.

Pregnancy, Lactation and Fertility:

The safety of the veterinary medicinal product has not been established in cattle and sheep during pregnancy, lactation or in animals intended for breeding. Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. Use only according to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:

No data available.

Overdose:

Cattle:
No symptoms other than those described in section 7.

Sheep:After administration of 3 times the recommended dose or more a transient reduction in feed and water consumption has been observed. Additional effects included an increased incidence of lethargy, emaciation and loose faeces.
Head tilt was seen after administration of 5 times the recommended dose and was considered most likely a result of irritation at the injection site.

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 rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1]; Loose stool[1]; Injection site inflammation[2], Injection site lesion[2]; Anaphylaxis (severe allergic reaction).

[1] Quick and complete recovery upon termination of treatment.
[2] May persist for 14 days after intramuscular and subcutaneous administration.

Sheep:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1]; Injection site inflammation[2], Injection site lesion[2].

[1] Quick and complete recovery upon termination of treatment.
[2] Mild and may persist up to 28 days after intramuscular administration.

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

For treatment
Cattle:
Intramuscular use: 20 mg/kg bodyweight (1 ml/15 kg) to be administered by intramuscular injection twice 48 hours apart using a 16 gauge needle.
Subcutaneous use: 40 mg/kg bodyweight (2 ml/15 kg) to be administered once only using a 16 gauge needle.

Sheep:
Intramuscular use: 20 mg /kg bodyweight (1 ml/15 kg bodyweight) to be administered daily for three consecutive days.
Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 μg/ml) for up to 18 hours after administration of the product at the recommended treatment dose. The pre-clinical data provided supported the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 μg/ml.

For metaphylaxis
Cattle:
Subcutaneous use: 40 mg/kg bodyweight (2ml/15kg) to be administered once only using a 16 gauge needle.

9. Advice on correct administration

The dose volume given at any one injection site should not exceed 10 ml for cattle and 4 ml for sheep.
The injection should only be given in the neck.
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.
The vials should not be broached more than 20 times. User should therefore select the most appropriate vial size according to the target species to be treated.
When treating groups of animals at the same time, use of a draw-off needle in the vial stopper is recommended to avoid excess stopper broaching. The draw-off needle should be removed after treatment.

10. Withdrawal periods

Meat and offal:

Cattle:	IM (20 mg/kg bodyweight, twice):	30 days.
	SC (40 mg/kg bodyweight, once):	44 days.
Sheep:		39 days.

Milk:
Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.

11. Special storage precautions

Keep out of the sight and reach of children.

Do not store above 25 °C.
Do not refrigerate.
Protect from frost.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 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

Pack sizes: 50, 100 and 250 ml vials.
Not all pack sizes may be marketed.
{< > MA no. to be adjusted nationally}

15. Date on which the package leaflet was last revised

{MM/YYYY}
{< > to be adjusted nationally}

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

<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}