ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cefa Safe 300 mg Intramammary Suspension for dairy cows at drying-off (AT, BE, CY, CZ, EE, EL, HU, HR, IT, LT, LU, LV, PT, RO, SK)
CepraShort 300 mg Intramammary Suspension for dairy cows at drying-off (IE, UK)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml intramammary syringe contains:

Active substance:
Cefapirin 300 mg
(equivalent to 383.3 mg cefapirin benzathine)

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intramammary suspension.
Creamy, oily suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (Dairy cow at drying-off)

4.2 Indications for use, specifying the target species

For the treatment of subclinical mastitis at drying-off caused by *Staphylococcus aureus,* coagulase-negative staphylococci*, Streptococcus agalactiae, Streptococcus dysgalactiae* and *Streptococcus uberis* susceptible to cefapirin.

4.3 Contraindications

Do not administer to animals which are known to be hypersensitive to cephalosporins, other beta-lactam antibiotics or to any of the excipients.
Do not use in animals suffering from severe renal disease.
In animals suffering from renal impairment use only following a benefit/risk assessment performed by the responsible veterinarian.
Do not use in cows with clinical mastitis.
Please refer also to section 4.7.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to cefapirin and may decrease the effectiveness of treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used.

The efficacy of the product is only established against the pathogens mentioned in Section 4.2 Indications for use. Consequently, serious acute mastitis (potentially fatal) due to other pathogen species, particularly *Pseudomonas aeruginosa*, can occur after drying off. Good hygienic practices should be thoroughly respected in order to reduce this risk.

Do not use the cleaning towel if lesions are present on the teat.

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

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillin may lead to cross sensitivity to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
People with known hypersensitivity to penicillins or cephalosporins should avoid contact with the veterinary medicinal product.
If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.

Wash hands after using the cleaning towels. People with known hypersensitivity to isopropyl alcohol should avoid direct contact with the cleaning towels. Avoid eye contact since Isopropyl alcohol may cause eye irritation.

4.6 Adverse reactions (frequency and seriousness)

Allergic reactions have been observed very rarely.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Do not use during lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Simultaneous parenteral administration of nephrotoxic substances (e.g. aminoglycoside and polypeptide antibiotics) may prolong excretion of cefapirin.

Concomitant use of cephalosporins and nephrotoxic drugs may increase renal toxicity.

Cephalosporins should not be administered concurrently with bacteriostatic antimicrobials.

4.9 Amounts to be administered and administration route

For single intramammary use only.
The contents of one syringe should be infused into the teat canal of each quarter immediately after the last milking of the lactation. Before infusion, the teat should be thoroughly cleaned and disinfected with the cleaning towel provided.
Remove the cap fully by holding the barrel of the syringe firmly in one hand and push up the cap with the thumb along the length of the cap until the cap clicks off. Take care not to contaminate the nozzle. Do not bend the nozzle.
Insert the nozzle into the teat canal and infuse the contents of one syringe.

Holding the end of the teat with one hand, gently massage upwards with the other hand to aid dispersion of the antibiotic into the quarter.
The intramammary syringe must only be used once.

After treatment, it is recommended to dip the teats in an appropriate disinfectant solution.

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

None known.

4.11 Withdrawal period(s)

Milk: 24 hours after calving if the interval between treatment and calving is 32 days or longer.
33 days after treatment if the interval between treatment and calving is less than 32 days.
Meat and offal: 14 days

The udder of treated cows must not be used for human consumption during the dry period and the following lactation period.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for intramammary use, first-generation cephalosporins
ATC vet code: QJ51DB08.

5.1 Pharmacodynamic properties

Cefapirin is bactericidal with a time dependant mechanism of action and is characterised by its broad therapeutic spectrum of activity. Cefapirin is a first-generation cephalosporin which acts via inhibition of the synthesis of bacterial cell walls. There is low cross-allergy between cephalosporins and penicillins (6 to 16%).
Three mechanisms of resistance to cephalosporin are known so far: reduced permeability of the cell wall, enzymatic inactivation and change of specific penicillin binding sites. In Gram-positive bacteria and particularly staphylococci, the main cephalosporin resistance mechanism is through alteration of penicillin binding proteins. Resistance of Gram-negative bacteria resistance consist largely in the production of β-lactamases.

Cefapirin is usually effective against *Staphylococcus aureus* (including penicillinase positive strains), coagulase negative staphylococci, *Streptococcus agalactiae* and *uberis.*

The resistance situation against *Streptococci* remains favourable while for Staphylococci the resistance situation can be more variable between geographical regions or individual herds.

An overview of the MIC_{50} and MIC_{90} values of the targeted mastitis pathogens collected in Europe between 2015 and 2016 by the VetPath programme of the European Animal Health Study Centre (CEESA) can be summarised as follows:

Bacteria	**No. of strains**	**MIC_{50}**	**MIC_{90}**
S. aureus	247	0.25	0.25
Coagulase negative staphylococci	189	0.12	0.25
S. agalactiae	33*	0.12	0.25
S. dysgalactiae	132	≤0.03	≤0.03
S. uberis	208	0.25	0.25

5.2 Pharmacokinetic particulars

At treatment during the dry period, therapeutically effective cefapirin concentrations in milk are maintained for at least 7 days. Protein binding in milk is 60 – 75%.
Maximum blood levels of 0.04 to 0.32 µg/ml were measured after 4 to 6 hours. Blood concentrations declined to below the limit of detection after 48 hours. The main metabolite of cefapirin is desacetyl-cefapirin, which is microbiologically active. After resorption from the udder, parent substance and metabolite are mainly excreted via the kidneys; to a lesser extend via the bile, and, after the start of the lactation period, also with the milk. Cefapirin concentrations above 0.02 µg/ml have been found in urine for up to 20 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium stearate
Arachis oil, refined

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years

6.4. Special precautions for storage

Do not store above 25 °C. Protect from light.

6.5 Nature and composition of immediate packaging

Pre-filled polyethylene syringe consisting of white low density polyethylene (LDPE) barrel with white LDPE plunger and light blue LDPE protective cap with 10 ml suspension for intramammary use and cleaning towels in a sachet consisting of paper/PE/Alu/sealing layer.

Pack sizes:
Cardboard box of 20 syringes and 20 cleaning towels.
Plastic bucket of 144 syringes and 144 cleaning towels.

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
Box and bucket

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cefa Safe 300 mg Intramammary Suspension for dairy cows at drying-off (AT, BE, CY, CZ, EE, EL, HU, HR, IT, LT, LU, LV, PT, RO, SK)
CepraShort 300 mg Intramammary Suspension for dairy cows at drying-off (IE, UK)
Cefapirin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 10 ml intramammary syringe contains:
Active substance:
Cefapirin 300 mg
(equivalent to 383.3 mg cefapirin benzathine)

3. PHARMACEUTICAL FORM

Intramammary suspension.

4. PACKAGE SIZE

20 intramammary syringes

144 intramammary syringes

5. TARGET SPECIES

Cattle (Dairy cow at drying-off).

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period(s):
Milk: 24 hours after calving if the interval between treatment and calving is 32 days or longer.
33 days after treatment if the interval between treatment and calving is less than 32 days.
Meat and offal: 14 days

The udder of treated cows must not be used for human consumption during the dry period and the following lactation period.

9. SPECIAL WARNING(S), IF NECESSARY

Penicillins and cephalosporins may occasionally cause severe allergic reactions. See package leaflet for user warnings.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Protect from light.

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

Read the package leaflet before use.

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

Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Syringe

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cefa Safe (AT, BE, CY, CZ, EE, EL, HU, HR, IT, LT, LU, LV, PT, RO, SK)
CepraShort (IE, UK)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Cefapirin 300 mg

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

10 ml

4. ROUTE(S) OF ADMINISTRATION

Intramammary

5. WITHDRAWAL PERIOD(S)

Withdrawal period(s):
Milk: 24 hours after calving if the interval between treatment and calving is 32 days or longer.
33 days after treatment if the interval between treatment and calving is less than 32 days.
Meat and offal: 14 days

The udder of treated cows must not be used for human consumption during the dry period and the following lactation period.

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Cefa Safe 300 mg Intramammary Suspension for dairy cows at drying-off)

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

Marketing authorisation holder:
Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

Manufacturer responsible for batch release:
Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cefa Safe 300 mg Intramammary Suspension for dairy cows at drying-off (AT, BE, CY, CZ, EE, EL, HU. HR. IT, LT, LU, LV, PT, RO, SK)
CepraShort 300 mg Intramammary Suspension for dairy cows at drying-off (IE, UK)
Cefapirin

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each 10 ml intramammary syringe contains:

Active substance:
Cefapirin 300 mg
(equivalent to 383.3 mg cefapirin benzathine)
Creamy, oily suspension

4. INDICATION(S)

For the treatment of subclinical mastitis at drying-off caused by *Staphylococcus aureus,* coagulase-negative staphylococci*, Streptococcus agalactiae, Streptococcus dysgalactiae* and *Streptococcus uberis* susceptible to cefapirin.

5. CONTRAINDICATIONS

Do not administer to animals which are known to be hypersensitive to cephalosporins, other beta-lactam antibiotics or to any of the excipients.
Do not use in animals suffering from severe renal disease.
In animals suffering from renal impairment use only following a benefit/risk assessment performed by the responsible veterinarian.
Do not use in cows with clinical mastitis.
Please refer also to section 12.

6. ADVERSE REACTIONS

Allergic reactions have been observed very rarely.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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 inform your veterinary surgeon.
Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Cattle (Dairy cow at drying-off)

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For single intramammary use only.
Administer 300 mg of cefapirin (the contents of one syringe) into each quarter, via the intra-mammary route.

9. ADVICE ON CORRECT ADMINISTRATION

The contents of one syringe should be infused into the teat canal of each quarter immediately after the last milking of the lactation. Before infusion, the teat should be thoroughly cleaned and disinfected with the cleaning towel provided. Remove the cap fully by holding the barrel of the syringe firmly in one hand and push up the cap with the thumb along the length of the cap until the cap clicks off. Take care not to contaminate the nozzle. Do not bend the nozzle.
Insert the nozzle into the teat canal and infuse the contents of one syringe.

Holding the end of the teat with one hand, gently massage upwards with the other hand to aid dispersion of the antibiotic into the quarter.
The intramammary syringe must only be used once.

After treatment, it is recommended to dip the teats in an appropriate disinfectant solution.

10. WITHDRAWAL PERIOD(S)

Milk: 24 hours after calving if the interval between treatment and calving is 32 days or longer.
33 days after treatment if the interval between treatment and calving is less than 32 days.
Meat and offal: 14 days

The udder of treated cows must not be used for human consumption during the dry period and the following lactation period.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 25 °C. Protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton or bucket after {EXP}. The date refers to the last day of that month."

12. SPECIAL WARNING(S)

Special precautions for use in animals

Use of the product should be based on susceptibility testing of the bacteria isolated form the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to cefapirin and may decrease the effectiveness of treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used.

The efficacy of the product is only established against the pathogens mentioned in Section 4.2 Indications for use. Consequently, serious acute mastitis (potentially fatal) due to other pathogen species, particularly *Pseudomonas aeruginosa*, can occur after drying off. Good hygienic practices should be thoroughly respected in order to reduce this risk.

Do not use the cleaning towel if lesions are present on the teat.

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

Penicillins and cephalosporins may cause allergy (hypersensitivity) following injection, inhalation, ingestion or skin contact. These reactions are occasionally serious. Hypersensitivity to penicillin may lead to cross sensitivity to cephalosporins and vice versa. People with known hypersensitivity to penicillins or cephalosporins should avoid contact with the veterinary medicinal product.
If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.

Wash hands after using the cleaning towels. People with known hypersensitivity to isopropyl alcohol should avoid direct contact with the cleaning towels. Avoid eye contact since Isopropyl alcohol may cause eye irritation.

Lactation:
Do not use during lactation.

Interaction with other medicinal products and other forms of interaction:
Simultaneous parenteral administration of nephrotoxic substances (e.g. aminoglycoside and polypeptide antibiotics) may prolong excretion of cefapirin.
Concomitant use of cephalosporins and nephrotoxic drugs may increase renal toxicity
Cephalosporins should not be administered concurrently with bacteriostatic antimicrobials.

Overdose (symptoms, emergency procedures, antidotes)

None known.

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

Medicines should not be disposed of via wastewater or household waste. Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Box of 20 syringes and 20 cleaning towels.
Bucket of 144 syringes and 144 cleaning towels.