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

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, EL, HU, HR, IT, LU, PT, RO, SK)
CepraShort 300 mg Intramammary Suspension for dairy cows at drying-off (IE, UK(NI))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml intramammary syringe contains:

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

Excipients:

Qualitative composition of excipients and other constituents
Aluminium stearate
Arachis oil, refined

Creamy, oily suspension.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (Dairy cow at drying-off)

3.2 Indications for use for each 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.

3.3 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.
Do not use in cows with clinical mastitis.
Please refer also to section 3.7.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

In animals suffering from renal impairment use only following a benefit/risk assessment performed by the responsible veterinarian.

Use of the veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal product is only established against the pathogens mentioned in Section 3.2. 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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (Dairy cow at drying-off):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Allergic reaction

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.

3.7 Use during pregnancy, lactation or lay

Lactation:
Do not use during lactation.

3.8 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.

3.9 Administration routes and dosage

Intramammary use.
For single 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.

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

None known.

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

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.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code : QJ51DB08

4.2 Pharmacodynamics

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

4.3 Pharmacokinetics

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 extent 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

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

5.3 Special precautions for storage

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

5.4 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.

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

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

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

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

{DD/MM/YYYY}

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

CARDBOARD BOX and PLASTIC BUCKET

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Cefapirin 300 mg (equivalent to 383.3 mg cefapirin benzathine)/10 ml intramammary syringe

3. PACKAGE SIZE

20 intramammary syringes
144 intramammary syringes

4. TARGET SPECIES

Cattle (Dairy cow at drying-off).

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramammary use.

7. WITHDRAWAL PERIODS

Withdrawal periods:
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.

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

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

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

Read the package leaflet before use.

Penicillins and cephalosporins may occasionally cause severe allergic reactions.

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

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INTRAMAMMARY SYRINGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Cefapirin 300 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

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

2. Composition

Each 10 ml intramammary syringe contains:

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

3. Target species

Cattle (Dairy cow at drying-off)

4. Indications for use

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.
Do not use in cows with clinical mastitis.
Please refer also to section ”Special warnings”.

6. Special warnings

Special precautions for safe use in the target species:
In animals suffering from renal impairment use only following a benefit/risk assessment performed by the responsible veterinarian.
Use of the veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal product is only established against the pathogens mentioned in Section “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.

7. Adverse events

Cattle (Dairy cow at drying-off):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):
Allergic reaction

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}

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

Intramammary use.
For single 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 periods

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 expiry date refers to the last day of that month.

12. Special precautions for disposal

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 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.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

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.

Box of 20 syringes and 20 cleaning towels.

Bucket of 144 syringes and 144 cleaning towels.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/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:

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

Local representatives and contact details to report suspected adverse reactions:

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