ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepebiotic 330 mg/100 mg intramammary solution for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml injector contains:

Active substances:
330 mg lincomycin as lincomycin hydrochloride
100 mg neomycin as neomycin sulphate (equivalent to 100 000 IU)

Excipients:

Qualitative composition of excipients and other constituents
Disodium edetate
Hydrochloric acid
Sodium hydroxide
Water for injections

Yellowish, aqueous solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

For the treatment of clinical mastitis in lactating cattle caused by: *Staphylococcus aureus* (both penicillinase and non-penicillinase producing strains), *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, and *Escherichia coli*.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance(s) or to any of the excipient(s).
Do not use in case of impaired kidney and liver function and in case of hearing and balance disorders.

3.4 Special warnings

There is complete cross-resistance between lincomycin and clindamycin; partial cross-resistance to macrolide antibiotics such as erythromycin, kitasamycin, spiramycin and oleandomycin.
Use of the antimicrobial should be carefully considered when susceptibility testing has shown resistance to lincosamides or aminoglycosides because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

The feeding of waste milk containing residues of lincomycin and neomycin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

This antimicrobial combination should only be used where diagnostic testing has indicated the need for simultaneous administration of each of the active substances.

Particular care should be taken when using the veterinary medicinal product in nursing animals, as gastrointestinal side effects of lincomycin may occur in suckling calves.

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

Aminoglycosides, such as neomycin, and lincosamides, such as lincomycin, may cause hypersensitivity (allergy) following ingestion or skin contact. Allergic reactions to these substances may occasionally be serious.
People with known hypersensitivity to aminoglycosides or lincosamides should avoid contact with this veterinary medicinal product.
Handle this veterinary medicinal product with great care to avoid exposure. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product. Do not smoke, eat or drink during use of the product.
In case of contact with the skin or eyes, wash immediately with water. If you develop symptoms following exposure, such as a skin rash or persisting eye irritation, seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Undetermined frequency (cannot be estimated from the available data)	Balance impaired[1], Impaired hearing[1] Renal disorder[1] Neuromuscular disorder (neuromuscular blockage)[1] Allergic skin reaction, Anaphylaxis

[1]particularly in animals with pre-damaged udder tissue

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 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

Can be used during pregnancy and lactation.

3.8 Interaction with other medicinal products and other forms of interaction

This veterinary medicinal product should not be used together with macrolides such as erythromycin, because lincomycin and macrolides can antagonise each other's effect at the site of action, the 50S subunit of the ribosome.

When used concomitantly with anaesthetics or agents with neuromuscular blocking effects (e.g. tubocurarine, gallamine, pancuronium), lincomycin enhances the curare-like effects of these muscle relaxants.

3.9 Administration routes and dosage

Intramammary use.

Three times administration of 1 injector per infected quarter with an interval of 12 hours.
Necessary precautions regarding asepsis should be taken. If necessary, wash the teat(s) or the entire udder thoroughly with warm water and a suitable antiseptic and dry thoroughly. Milk the quarter completely. Disinfect the teat orifice with an alcohol pad or other suitable disinfectant. Use a new cloth for each teat. Remove the cap from the plastic injector. Insert the tip of the injector in the teat canal and cistern. Completely press the plunger down to instill the full content of the injector, then gently massage the quarter to get the veterinary medicinal product into the milk cistern. After instillation, it is recommended to disinfect all teats with a suitable dipping agent.

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

There are no known effects of overdose.

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: 3 days.
Milk: 84 hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ51RF03

4.2 Pharmacodynamics

Lincomycin is a lincosamide antibiotic produced by *Streptomyces lincolnensis*. Lincomycin has specific activity against Gram-positive bacteria, including staphylococci and streptococci, and has little activity against Gram-negative bacteria such as *E. Coli*. The molecule is also active against anaerobic bacteria. Lincomycin binds to the 50S subunit of the bacterial ribosome, inhibiting the cell's protein synthesis. The mechanism of action is bacteriostatic.
Neomycin is an aminoglycoside antibiotic, produced by *Streptomyces fradiae*.

Neomycin has a broad-spectrum activity against both Gram-positive bacteria, including staphylococci and streptococci, and Gram-negative bacteria, including *E. coli*. The activity against staphylococci is higher than that against streptococci. Neomycin binds to the 30S subunit of the bacterial ribosome, resulting in an inhibition of protein synthesis. At high concentrations, the aminoglycosides also damage the cell membrane of the bacteria and their mechanism of action is therefore generally referred to as both bacteriostatic and bactericidal.
In vitro studies have shown that the combination of lincomycin and neomycin has a bactericidal mechanism of action against *Staphylococcus aureus* and *Escherichia coli* and a bacteriostatic mechanism of action against streptococci. Synergy was also demonstrated against *Staphylococcus aureus* for this combination. Lincomycin and neomycin, as well as the combination of both are active against both penicillinase and non-penicillinase producing staphylococci.

Resistance development against lincosamides is mainly a result of methylation of adenine residues in the 23S ribosomal RNA of the 50S ribosomal subunit, which prevents drug binding to the target site. The rRNA methylases are encoded by erythromycin-resistant methylase (*erm*) genes. The *erm* genes are acquired through mobile elements and can be located on the bacterial chromosome or on plasmids. Other mechanisms of resistance to lincosamides involve enzymatic inactivation and active efflux of the drug.

For aminoglycosides the most clinically important resistance is caused by plasmid-mediated enzymes. These enzymes modify aminoglycosides at their exposed hydroxyl or amino groups to prevent ribosomal binding. Plasmid-mediated resistance to aminoglycosides is transferable between bacteria. Chromosomal mutation resulting in resistance is relatively unimportant except for streptomycin and dihydrostreptomycin. Chromosomal resistance develops slowly, because there are many 30S ribosomal binding sites.

4.3 Pharmacokinetics

After administration of the veterinary medicinal product according to the recommended treatment schedule, the following concentrations of lincomycin and neomycin were measured in the treated quarters:

Antibiotic	Concentration (mg/ml) / Time after first administration			
	12 hours[1]	24 hours[2]	36 hours	48 hours
Lincomycin	52.7	53.5	56.9	6.1
Neomycin	27.2	29.9	28.0	4.9

[1] immediately before second administration
[2] immediately before third (last) administration

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: 30 months.

5.3 Special precautions for storage

Store below 30ºC.

5.4 Nature and composition of immediate packaging

LLDPE injectors with 10 ml solution each.

Pack size:
Cardboard box with 4, 12, 24, 48 or 144 injectors.
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

CP-Pharma Handelsgesellschaft mbH

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

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

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepebiotic 330 mg/100 mg intramammary solution

2. STATEMENT OF ACTIVE SUBSTANCES

330 mg lincomycin as lincomycin hydrochloride
100 mg neomycin as neomycin sulphate (equivalent to 100 000 IU)

3. PACKAGE SIZE

10 ml

4. TARGET SPECIES

Cattle

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramammary use.

7. WITHDRAWAL PERIODS

Withdrawal periods:
Meat and offal: 3 days.
Milk: 84 hours.

8. EXPIRY DATE

Exp. mm/yyyy

9. SPECIAL STORAGE PRECAUTIONS

Store below 30ºC.

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

CP-Pharma Handelsgesellschaft mbH.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Injector

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepebiotic

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

10 ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Cepebiotic 330 mg/100 mg intramammary solution for cattle

2. Composition

Each 10 ml injector contains:

Active substances:
330 mg lincomycin as lincomycin hydrochloride
100 mg neomycin as neomycin sulphate (equivalent to 100 000 IU)

Yellowish, aqueous solution.

3. Target species

Cattle

4. Indications for use

For the treatment of clinical mastitis in lactating cattle caused by: *Staphylococcus aureus* (both penicillinase and non-penicillinase producing strains), *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, and *Escherichia coli*.

5. Contraindications

Do not use in cases of hypersensitivity to the active substance(s) or to any of the excipient(s).
Do not use in case of impaired kidney and liver function and in case of hearing and balance disorders.

6. Special warnings

Special warnings:

There is complete cross-resistance between lincomycin and clindamycin; partial cross-resistance to macrolide antibiotics such as erythromycin, kitasamycin, spiramycin and oleandomycin.
Use of the antimicrobial should be carefully considered when susceptibility testing has shown resistance to lincosamides or aminoglycosides because its effectiveness may be reduced.

Special precautions for safe use in the target species:

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

The feeding of waste milk containing residues of lincomycin and neomycin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

This antimicrobial combination should only be used where diagnostic testing has indicated the need for simultaneous administration of each of the active substances.

Particular care should be taken when using the veterinary medicinal product in nursing animals, as gastrointestinal side effects of lincomycin may occur in suckling calves.

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

Aminoglycosides, such as neomycin, and lincosamides, such as lincomycin, may cause hypersensitivity (allergy) following ingestion or skin contact. Allergic reactions to these substances may occasionally be serious.
People with known hypersensitivity to aminoglycosides or lincosamides should avoid contact with this veterinary medicinal product.
Handle this veterinary medicinal product with great care to avoid exposure. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product. Do not smoke, eat or drink during use of the product.
In case of contact with the skin or eyes, wash immediately with water. If you develop symptoms following exposure, such as a skin rash or persisting eye irritation, seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation:

Can be used during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:

This veterinary medicinal product should not be used together with macrolides such as erythromycin, because lincomycin and macrolides can antagonise each other's effect at the site of action, the 50S subunit of the ribosome.

When used concomitantly with anaesthetics or agents with neuromuscular blocking effects (e.g. tubocurarine, gallamine, pancuronium), lincomycin enhances the curare-like effects of these muscle relaxants.

Overdose:

There are no known effects of overdose.

Major incompatibilities:

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

7. Adverse events

Undetermined frequency (cannot be estimated from the available data)	Balance impaired[1], Impaired hearing[1] Renal disorder[1]

	Neuromuscular disorder (neuromuscular blockage)[1] Allergic skin reaction, Anaphylaxis

[1]particularly in animals with pre-damaged udder tissue

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 using the contact details at the end of this leaflet, or via your national reporting system.

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

Intramammary use.

Three times administration of 1 injector per infected quarter with an interval of 12 hours.
Necessary precautions regarding asepsis should be taken.

9. Advice on correct administration

If necessary, wash the teat(s) or the entire udder thoroughly with warm water and a suitable antiseptic and dry thoroughly. Milk the quarter completely. Disinfect the teat orifice with an alcohol pad or other suitable disinfectant. Use a new cloth for each teat. Remove the cap from the plastic injector. Insert the tip of the injector in the teat canal and cistern. Completely press the plunger down to instill the full content of the injector, then gently massage the quarter to get the veterinary medicinal product into the milk cistern. After instillation, it is recommended to disinfect all teats with a suitable dipping agent.

10. Withdrawal periods

Meat and offal: 3 days.
Milk: 84 hours.

11. Special storage precautions

Keep out of the sight and reach of children.

Store below 30ºC.
Do not use this veterinary medicinal product after the expiry date which is stated on the label and outer packaging 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 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

Packed as 4, 12, 24, 48 and 144 injectors in outer cardboard box.
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

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 events:
CP-Pharma Handelsgesellschafft mbH
Ostlandring 13
31303 Burgdorf
Germany
Tel: +49-(0)5136-6066-0

Local representatives and contact details to report suspected adverse events:

17. Other information