ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LINEOMAM LC 330 mg/10 ml + 100,000 IU/10 ml intramammary solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each intramammary syringe (10 ml) contains:

Active substances:

Lincomycin	330 mg (equivalent to 359.6 mg lincomycin hydrochloride)
Neomycin sulfate	100,000 IU

Excipients:

Disodium edetate	4.98 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intramammary solution.
A clear, colourless to yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (lactating dairy cows).

4.2 Indications for use, specifying the target species

Treatment of mastitis caused by *Staphylococcus* spp., including *S. aureus*, *Streptococcus* spp. including *S. agalactiae, S. dysgalactiae* and *S. uberis*, and coliform bacteria, including *E. coli* susceptible to a combination of lincomycin and neomycin in dairy cows during lactation.

4.3 Contraindications

Do not use in cases of known hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Official national and regional antimicrobial policies should be taken into account when the product is used. Increasing trend in prevalence of resistance to lincomycin in *Streptococcus uberis* and *Staphylococcus aureus* isolated from bovine mastitis has been detected in some EU countries. The use of the product should be based on susceptibility testing of the bacteria isolated from the diseased animals from the respective farm. 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 this Summary of Product Characteristics may increase the prevalence of bacteria resistant to lincomycin or neomycin and may decrease the effectiveness of treatment with macrolides and other lincosamides or aminoglycosides due to the potential for cross resistance.
Do not use the disinfection towels on teats with lesions.

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

Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.

Handle this product with great care to avoid exposure, taking all recommended precautions.
Personal protective equipment consisting of rubber gloves should be worn when handling the veterinary medicinal product.
In case of accidental contact with skin, wash the affected area immediately with soap and water.
In case of contact with eyes, rinse immediately with plenty of water.
Wash hands after use.
Wash hands after use of disinfectant wipes and use protective gloves in case of known hypersensitivity to isopropyl alcohol.

4.6 Adverse reactions (frequency and seriousness)
None known.

4.7 Use during pregnancy, lactation
Can be used during pregnancy.
The product is intended to be used during lactation.

4.8 Interaction with other medicinal products and other forms of interaction
This product should not be used concomitantly with macrolides. Lincomycin and macrolides antagonise each other due to competition for the binding site on the 50S ribosomal subunit, which is the target site for the antimicrobial action of both the molecules.
Aminoglycosides are synergistic with some beta-lactam antibiotics. Synergism is given by, among other things, the damage of the bacterial cell wall caused by the action of beta-lactams, allowing the easier penetration of aminoglycoside to the target structure of the bacterial ribosome. Such mechanism was described in streptococci and Gram-negative bacteria.

4.9 Amounts to be administered and administration route
For intramammary use.
For one dose, the content of 1 applicator is administered to each affected quarter, i.e. 100,000 IU neomycin sulphate and 330 mg lincomycin. Doses are repeated at 12-hour intervals. A total of 3 doses are administered to each affected quarter.

Administer the product by intramammary infusion only, taking aseptic precautions. Infuse to a clean, washed and thoroughly dried udder, as soon as possible after complete milking of the treated quarter. Prior to administration, disinfect the end of the teat using one of the disinfectant towels provided (use a new towel for each teat!).
Prior to administration, hold the applicator with the cannula pointed upward and remove the cap from the cannula in this position. Immediately after opening, insert the cannula into the teat canal, press the plunger and infuse the entire contents of the applicator into the affected quarter. Following administration, it is recommended to massage the teat shortly, from the tip of the teat towards the milk cistern.
Each applicator is intended for single use only.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
The product is well tolerated. In case of accidental overdose, any local or systemic adverse reactions are not expected to occur.

4.11 Withdrawal period(s)
Meat and offal: 3 days.
Milk: 84 hours.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for intramammary use, lincomycin, combinations with other antibacterials.
ATC vet code: QJ51RF03.

5.1 Pharmacodynamic properties

Neomycin is a three-component aminoglycoside antibiotic, with a majority of neomycin B, produced by strains of *Streptomyces fradiae*. Neomycin has a broad activity spectrum of activity, in Gram-negative germs it acts against enterobacteria including *E. coli*. From Gram-positive bacteria, non-penicillinase-producing *Staphylococcus aureus* strains, coagulase-negative *Staphylococcus* spp. strains and *Mycobacterium* spp. strains are susceptible to neomycin. Anaerobic bacteria are naturally resistant.
The effect consists in binding to the 30S subunit of the bacterial ribosome. Change in the ribosome configuration affects the translation process with subsequent impairment of protein synthesis. High concentrations damage the bacterial cell membrane. Neomycin may have a bactericidal effect. Aminoglycosides have a significant post-antibiotic effect (PAE). This is shown at the stage where the concentration of antibiotic will drop below the level of MIC pathogenic, but bacteria damaged by the antibiotic are susceptible to immune processes of the host, and thus may be killed.

Lincomycin is a lincosamide antibiotic produced by *Streptomyces lincolnensis*.
It provides a specific activity against Gram-positive bacteria, especially *Staphylococcus* spp. and S*treptococcus* spp., and against mycoplasma. Conversely, it has low or no activity against Gram-negative bacteria, except for anaerobes.
The mode of action consists of binding to the 50S subunit of the bacterial ribosome, specifically to 23S rRNA in location A2028. This inhibits protein synthesis (elongation phase). The effect is bacteriostatic.

In vitro studies demonstrated that lincomycin and neomycin in combination have bactericidal activity against *S. aureus* and bacteriostatic activity against streptococci. The synergy against *S. aureus* was demonstrated for combination.
Lincomycin, neomycin and their combination have been shown to be active against both penicillinase and non-penicillinase producing staphylococci.

Four main mechanisms of resistance have been demonstrated yet in the strains resistant to aminoglycosides, including neomycin: (i) formation of inactivating enzymes (encoded by *aph*, *aac*, *ant* genes), (ii) alteration of absorption of the antibiotic in a bacterial cells, (iii) utilisation of active efflux, (iv) alteration of the ribosomal target site.
The genes *aph*, *aac*, *ant* can be carried chromosomally or extrachromosomally on mobile genetic elements.

Four main mechanisms of resistance have been demonstrated yet in the strains resistant to lincosamides, including lincomycin: (i) alteration of the ribosomal target site (encoded by *erm* genes), (ii) utilisation of active efflux (*msr*, *vga* and *lsa* genes), (iii) formation of inactivating enzymes (encoded by *lnu* genes), (iv) mutation of the ribosomal target site. There is a cross resistance to macrolides, lincosamides and streptogramin B, referred to as MLS_B. The strains with MLS_B resistance have 2 phenotypic manifestations: constitutive ($cMLS_B$) and inducible ($iMLS_B$). To demonstrate the $iMLS_B$ phenotype it is recommended to carry out the so-called D-test with clindamycin, which is also a substrate for routine susceptibility testing.
Genes *erm* are located on mobile genetic elements (plasmids, transposons), or spread vertically as chromosomal mutations. The genes encoding active efflux are carried chromosomally in Gram-negative bacteria, or carried on the plasmids in Gram-positive bacteria. Genes *lnu* are carried on plasmids.

5.2 Pharmacokinetic particulars

After administration of the intramammary solution containing lincomycin and neomycin sulphate at the doses and intervals corresponding to the recommendations for administration of the product, the following concentrations of lincomycin and neomycin were measured in individual treated quarters:

	Time from the first administration			
	12 hrs *	24 hrs **	36 hrs	48 hrs
Antibiotic	Concentration [µg/ml] in milk			
Lincomycin	52.7	53.5	56.9	4.6
Neomycin	22.2	29.7	28.0	4.9

* Just before the second administration
** Just before the third (last) administration

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Hydrochloric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: use immediately.

6.4 Special precautions for storage

Protect from frost.
Protect from light.

6.5 Nature and composition of immediate packaging

LDPE applicators containing 10 ml of the product, with a LDPE cap and a LDPE plunger. 24 applicators packed in a carton. Each package includes 24 disinfectant towels moistened with 65% v/v isopropyl alcohol solution (2.4 ml/towel) to clean teats.

Pack size: 24 x 10 ml

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

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

Bioveta, a.s.
Komenského 212/12
683 23 Ivanovice na Hané
Czech Republic

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.