SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Combiclav Intramammary Suspension for Lactating Cows

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each intramammary syringe of 3g contains:

Active substances:

Amoxicillin (as amoxicillin trihydrate)	200 mg
Clavulanic acid (as potassium clavulanate)	50 mg
Prednisolone	10 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intramammary suspension
Cream to buff oily suspension

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (lactating cows)

4.2 Indications for use, specifying the target species

For the treatment of clinical mastitis caused by the following bacteria susceptible to the combination of amoxicillin and clavulanic acid:

Staphylococci (including β-lactamase producing strains)
Streptococci (including S. agalactiae, S. dysgalactiae and S. uberis)
Escherichia coli (including β-lactamase producing strains)

4.3 Contraindications

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

4.4 Special warnings for each target species

Do not use in cases associated with Pseudomonas.

4.5 Special precautions for use

Special precautions for use in animals
Swab teat end before treatment, with cleaning towels provided.

Recommendations for prudent use
The product should be used for treatment of clinical mastitis only.
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.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
The combination of amoxicillin and clavulanic acid should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.
Avoid use of the product in herds where no β-lactamase producing staphylococci strains have been isolated. E.coli mastitis with mild to moderate clinical signs, a non-antimicrobial approach should be the first option. Veterinarians should strive to use narrow spectrum antibiotics if possible. Inappropriate use of the product may increase the prevalence of bacteria resistant to β-lactam antibiotics and may decrease the effectiveness of treatment with β-lactam antibiotics, due to the potential for cross-resistance. Most of the ESBLs and AmpC β-lactamases producing E.coli strains may not be inhibited by the combination of amoxicillin/clavulanic acid.
The feeding of waste milk containing residues of antibiotics to calves should be avoided up to the end of the milk withdrawal period, except during colostral phase, because it could select antimicrobial resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This product may cause skin and eye irritation. Avoid contact with the skin and eyes. In the event of skin or eye contact rinse with plenty of clean water.
The cleaning towels supplied with the product contain isopropyl alcohol, which many cause skin or eye irritation in some people.
The wearing of gloves is recommended during administration of the product and when handling the cleaning towels.
Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion, or skin contact.
Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
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.
If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning.
Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.
Wash hands after use.

Other precautions
Due to the endocrine-disrupting potential of prednisolone, the product may be dangerous to fish and other aquatic organisms. Consequently treated animals should not have access to watercourses during the first 12 hours after treatment.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases, immediate hypersensitivity reactions may occur (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

No special precautions.

4.8 Interaction with other medicinal products and other forms of interaction

None known

4.9 Amounts to be administered and administration route

Intramammary use.
The syringe must only be used once. Partly emptied syringes due to the unsuccessful use should be discarded.
The content of one syringe should be infused gently into the teat of the infected quarter every 12 hours after each of three consecutive milkings.
Milk out the infected quarters. After thoroughly cleaning and disinfecting the teat and teat orifice with the cleaning towels provided, gently infuse the contents of one syringe into each affected quarter. Disperse the product by gentle massage of the teat and udder of the affected animal.
In cases of infections caused by Staphylococcus aureus, a longer course of antibacterial therapy may be required. Therefore overall treatment length must be at the veterinarian's discretion but should be long enough to ensure complete resolution of intramammary infection.

Combined therapy for the treatment of bovine mastitis. In the situation where systemic treatment as well as intramammary treatment is necessary, especially in cases of serious clinical mastitis Combiclav Injection can be administered in combination with this product.

For combined therapy the following minimum treatment regime should be followed:

Potentiated Penicillin Injection	Potentiated Penicillin Intramammary Suspension for Lactating Cows
Intramuscular injection at a dose rate of 8.75 mg/kg bodyweight (7,0 amoxicillin and 1,75 mg clavulanic acid) which corresponds to 1 ml of product/20 kg bodyweight daily for 3 days as follows: 8.75 mg/kg bodyweight (7.0 mg amoxicillin, 1.75 mg clavulanic acid) i.e. 1 ml/20 kg bodyweight 24 hours ↓ 8.75 mg/kg bodyweight (7.0 mg amoxicillin, 1.75 mg clavulanic acid) i.e. 1 ml/20 kg bodyweight 24 hours ↓ 8.75 mg/kg bodyweight (7.0 mg amoxicillin, 1.75 mg clavulanic acid) i.e. 1 ml/20 kg bodyweight Where necessary Potentiated Penicillin Injection may be administered for an additional two days for a total of 5 daily injections	The content of one syringe should be infused gently into the teat of the infected quarter every 12 hours after each of three consecutive milkings as follows: One syringe gently infused into the teat of the infected quarter 12 hours ↓ One syringe gently infused into the teat of the infected quarter 12 hours ↓ One syringe gently infused into the teat of the infected quarter

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

No adverse reactions are to be expected from an accidental overdose.

4.11 Withdrawal period(s)

Meat and offal: 7 days
Milk: 84 hours.

Combined Therapy:
When using this product and Combiclav Injection in combination:
Meat and offal: 42 days
Milk: 84 hours
From the last treatment of Combiclav Injection following the minimum posology regime.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for intramammary use – antibacterials and corticosteroids

ATC vet code: QJ51RV01

5.1 Pharmacodynamic properties

Amoxicillin is a broad spectrum bactericidal β-lactam antibiotic. Clavulanic acid inactivates β-lactamases. This combination is effective against β-lactamase producing organisms.

Prednisolone is an anti-inflammatory corticosteroid.

In vitro, clavulanic acid and amoxicillin in combination are active against a wide range of clinically important bacteria including the following organisms which are commonly associated with bovine mastitis:
Staphylococci (including β-lactamase producing strains)
Streptococci (including S. agalactiae, S. dysgalactiae and S. uberis)
Escherichia coli (including β-lactamase producing strains)

The Minimum Inhibitory Concentrations (MICs) of these target organisms determined from samples collected in nine EU countries (namely Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Spain, and the UK)1, show susceptibility to amoxicillin and clavulanic acid used in combination in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines2 on breakpoints (Table 1 and 2).

Table 1: Minimum Inhibitory Concentrations (mg/L) of Amoxicillin/Clavulanic Acid against strains from mastitis in dairy cattle in nine EU countries

	E. coli	*S. aureus*	*CNS*	*S. uberis*	*S. dysgalactiae*
Amoxicillin/Clavulanic Acid	8	1	0.5	0.5	≤0.03

Table 2: Clinical Laboratory Standards Institute (CLSI) resistance breakpoints (mg/L) for target bacteria

	E. coli	*S. aureus*	*CNS*[3]	*S. uberis*	*S. agalactiae*	*S. dysgalactiae*
Amoxicillin/Clavulanic Acid	≥32	≥8	≥8	≥32	≥8	≥32

1Antimicrobial susceptibility of mastitis pathogens isolated from diseased dairy cows across Europe: VetPath monitoring results, European society of clinical microbiology and infectious diseases (ECCMID), 2015.
2Clinical and Laboratory Standards Institute (2013). Approved standards- fourth edition, CLSI document VETO01-A4, Wayne, PA, USA.
3CNS – Coagulase Negative Staphylococci

The mechanisms underlying antimicrobial resistance in Streptococcus can be acquired through the mutation of intrinsic genes or horizontal exchange of genetic material encoding resistance determinants. Mastitic strains of E. coli and Staphylococcus, are known to acquire resistance through horizontal gene transfer and bacteriophages/plasmid transfer, and also through their ability to form a biofilm.

Acquired resistance prevalence in particular to be high in E. coli. In some strains of Staphylococcus aureus (methicillin-resistant S. aureus, MRSA), and of Staphylococcus pseudintermedius, resistance to all β-lactams is conferred by the alteration of the cell wall target proteins (penicillin-binding proteins). This is often associated with resistance to multiple other antimicrobial compounds with cross resistance.

Mastitic strains of E. coli and Staphylococcus are known to acquire resistance through horizontal gene transfer and bacteriophages/plasmid transfer, and also through their own ability to form a biofilm.

5.2 Pharmacokinetic particulars

It has been documented that the pharmacokinetic characteristics of penicillins (including amoxicillin) after intramammary administration indicate rapid elimination of the drug from milk. The mean residence time has a several-fold lower value than the designated elimination half-life and amounts to only 3.4 h. The concentration of the drug in the milk drop relatively quickly and the process is very dynamic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium Sodium Silicate
Cetostearyl Alcohol (Type B), emulsifying
Paraffin, White Soft
Paraffin, Light Liquid

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
Store in a dry place.

6.5 Nature and composition of immediate packaging

Single dose 3g white LDPE syringes with a white LDPE dual push-fit cap.

Cartons of 3, 12, and 24 syringes, or buckets of 120 syringes including 3, 12, 24, or 120 individually wrapped teat cleaning towels containing isopropyl alcohol.
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

Extremely dangerous for fish and aquatic life. Do not contaminate ponds, waterways or ditches with the product or used container.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Norbrook Laboratories Limited
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BT35 6JP
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 02000/4424

9. DATE OF FIRST AUTHORISATION

03 October 2018

10. DATE OF REVISION OF THE TEXT

March 2023

Approved 03 March 2023