1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Noroclav Intramammary Suspension for Lactating Cows [AT, BE, EE, FR, IE, LV, LT, LU, NL, RO, UK-NI]
Noroclav (200 mg + 50 mg + 10 mg)/3 g intramammary suspension for cattle [PL]
Anofline intramammális szuszpenzió tejelő teheneknek A.U.V. [HU]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each intramammary syringe of 3 g contains:

Active substances:

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

Excipients:

Qualitative composition of excipients and other constituents
Aluminium Sodium Silicate
Cetostearyl Alcohol (Type B), emulsifying
Paraffin, White Soft
Paraffin, Light Liquid

Cream to buff oily suspension.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (lactating cows).

3.2 Indications for use for each 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).

3.3 Contraindications

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

3.4 Special warnings

Do not use in cases associated with *Pseudomonas.*

3.5 Special precautions for use

Special precautions for safe use in the target species:

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. 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.
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 may 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 label or leaflet to the doctor.
Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.
Wash hands after use.

Special precautions for the protection of the environment:

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.

3.6 Adverse events

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

Pregnancy and lactation:

Can be used during pregnancy and lactation.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

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.

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

No adverse reactions are to be expected from an accidental 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: 7 days.
Milk: 84 hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ51RV01

4.2 Pharmacodynamics

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) guidelines[2] 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

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

4.3 Pharmacokinetics

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 hours. The concentration of the drug in the milk drops relatively quickly and the process is very dynamic.

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.
Store in a dry place.

5.4 Nature and composition of immediate packaging

Single dose 3 g white LDPE syringes with a white LDPE dual push-fit cap.
Cartons of 3, 12, and 24 syringes, including 3, 12 or 24 individually wrapped teat cleaning towels containing isopropyl alcohol , or buckets of 120 syringes including 120 individually wrapped teat cleaning towels containing isopropyl alcohol.
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.

Extremely dangerous for fish and aquatic life. Do not contaminate ponds, waterways or ditches with the product or used container.

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

{Cartons of 3, 12, or 24 syringes}
{Buckets of 120 syringes}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Noroclav Intramammary Suspension

2. STATEMENT OF ACTIVE SUBSTANCES

Each intramammary syringe of 3 g contains:

Amoxicillin	200 mg
Clavulanic Acid	50 mg
Prednisolone	10 mg

3. PACKAGE SIZE

3, 12, 24 or 120 syringes

4. TARGET SPECIES

Cattle (lactating cows).

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramammary use.

7. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: 7 days.
Milk: 84 hours.

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.
Store in a dry place.

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

Read the package leaflet before use.

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

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

{3 g Syringe label}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Noroclav

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Each intramammary syringe of 3 g contains:

Amoxicillin	200 mg
Clavulanic Acid	50 mg
Prednisolone	10 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Noroclav Intramammary Suspension for Lactating Cows

2. Composition

Each 3 g syringe contains:

Active substances:

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

Cream to buff oily suspension.

3. Target species

Cattle (lactating cows).

4. Indications for use

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

5. Contraindications

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

6. Special warnings

Special warnings:

For animal treatment only.

Special precautions for safe use in the target species:
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. 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.
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 may 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 label or leaflet to the doctor.
Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.
Wash hands after use.

Special precautions for the protection of the environment:

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.

Pregnancy and lactation:

Can be used during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:

None known.

Overdose:

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

Major incompatibilities:

Not applicable.

7. Adverse events

Very rare	Hypersensitivity reaction

(<1 animal / 10,000 animals treated, including isolated reports):	

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:

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

Intramammary use.

. 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.
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.

9. Advice on correct administration

Use each syringe only once.
Partly emptied syringes due to the unsuccessful use should be discarded.
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.

10. Withdrawal periods

Meat and offal: 7 days.
Milk: 84 hours.

11. Special storage precautions

Keep out of the sight and reach of children.

Do not store above 25 °C.
Store in a dry place.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton 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.

Extremely dangerous for fish and aquatic life. Do not contaminate ponds, waterways or ditches with the product or used container.

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

Single dose 3 g white LDPE syringes with a white LDPE dual push-fit cap.
Cartons of 3, 12, and 24 syringes, including 3, 12, or 24 individually wrapped teat cleaning towels containing isopropyl alcohol, or buckets of 120 syringes including 120 individually wrapped teat cleaning towels containing isopropyl alcohol.
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 contact details to report suspected adverse reactions>:
(EU)
Norbrook Laboratories (Ireland) Ltd.
Rossmore Industrial Estate
Monaghan
Ireland

(UK)
Norbrook Laboratories Limited
Station Works
Newry
Co. Down
BT35 6JP
United Kingdom

Manufacturer responsible for batch release:
Norbrook Manufacturing Ltd.
Rossmore Industrial Estate
Monaghan
Ireland

Norbrook Laboratories Limited
Station Works
Newry
Co. Down
BT35 6JP
United Kingdom

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.

17. Other information

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) guidelines[2] 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

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

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 hours. The concentration of the drug in the milk drops relatively quickly and the process is very dynamic.