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

Paraclav Intramammary Suspension for Lactating Cows

2. STATEMENT OF ACTIVE SUBSTANCES

Each intramammary syringe of 3 g contains:

Amoxicillin	200 mg
Clavulanic Acid	50 mg
Prednisolone	10 mg

3. PHARMACEUTICAL FORM

Intramammary suspension

4. PACKAGE SIZE

3, 12, 24 or 120 syringes

5. TARGET SPECIES

Cattle (lactating cows)

6. INDICATION(S)

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)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramammary use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

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

9. SPECIAL WARNING(S), IF NECESSARY

Penicillins and cephalosporins may cause hypersensitivity.
Read the package leaflet before use

10. EXPIRY DATE

EXP {day/month/year}

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

(EU)
Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
Ireland

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

Distributed by:

Norbrook Laboratories (GB) Ltd
1 Saxon Way East
Oakley Hay Industrial Estate
Corby
Northamptonshire
NN18 9EX
United Kingdom

16. MARKETING AUTHORISATION NUMBER(S)

Vm 02000/4426

17. MANUFACTURER'S BATCH NUMBER

Batch number

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{3 g Syringe label}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Paraclav Intramammary Suspension for Lactating Cows

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Each intramammary syringe of 3g contains:

Amoxicillin	200 mg
Clavulanic Acid	50 mg
Prednisolone	10 mg

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

3 g

4. ROUTE(S) OF ADMINISTRATION

Intramammary us

5. WITHDRAWAL PERIOD(S)

Meat: 7 days
Milk: 84 hours

6. BATCH NUMBER

Batch number

7. EXPIRY DATE

EXP {day/month/year}

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Paraclav Intramammary Suspension for Lactating Cows

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

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

(EU)
Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
Ireland

Manufacturer responsible for batch release:
(UK)
Norbrook Laboratories Limited
Station Works
Newry
Co. Down
BT35 6JP
United Kingdom

(EU)
Norbrook Manufacturing Ltd
Rossmore Industrial Estate
Monaghan
Ireland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Paraclav Intramammary Suspension for Lactating Cows

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each 3 g syringe contains:

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

Cream to buff oily suspension

4. INDICATION(S)

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. ADVERSE REACTIONS

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

7. TARGET SPECIES

Cattle (lactating cows)

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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.

9. ADVICE ON CORRECT ADMINISTRATION

Use each syringe only once.

10. WITHDRAWAL PERIOD(S)

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 stated on the label and carton after EXP.

12. SPECIAL WARNING(S)

For animal treatment only.

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. 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 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.

Pregnancy and lactation:
No special precautions.

Overdose (symptoms, emergency procedures, antidotes):
No adverse reactions are to be expected from an accidental overdose.

Interaction with other medicinal products and other forms of interaction
None known.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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 from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

June 2019

15. OTHER INFORMATION

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.

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 h. The concentration of the drug in the milk drop relatively quickly and the process is very dynamic.

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

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