SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synuclav Suspension for Injection (UK)
Clavobay Suspension Injectable (FR)
Noroclav Suspension for Injection (PT)
Noroclav 175 mg Suspension for Injection (ES)
Noroclav Injection (BE, IT)
Combisyn Injection (IS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml supplies:

Active Substance:

Amoxicillin (as Amoxicillin trihydrate)	140 mg
Clavulanic acid (as Potassium clavulanate)	35 mg

Excipients:

Butylated hydroxyanisole (E320)	0.08 mg
Butylated hydroxytoluene (E321)	0.08 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection.

An off-white to cream oily suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and Dogs.

4.2 Indications for use, specifying the target species

In Cattle:

- Treatment of mastitis
- Treatment of respiratory infections due to *Pasteurella multocida* and *Mannheimia haemolytica*.

In Dogs:
Respiratory tract infections, urinary tract infections, skin and soft tissue infections (e.g. abscesses, pyoderma, anal sacculitis and gingivitis

4.3 Contraindications

Do not use in animals with known hypersensitivity to penicillin or other substances of the beta-lactam group.

Do not use in animals with serious dysfunction of kidneys accompanied by anuria or oliguria.

Do not use in rabbits, guinea pigs, hamsters or gerbils.

The use of the product is contraindicated where resistance to the combination of penicillins or other substances of the beta-lactam group is known to occur.

4.4 Special Warnings for each target species

None.

4.5 Special precautions for use

i. Special precautions for use in animals

This product does not contain an antimicrobial preservative.

Clavulanic acid is moisture sensitive. It is very important therefore, that a completely dry needle and syringe is used when extracting suspension for injection in order to avoid contaminating the remaining contents of the vial with drops of water.

Contamination will result in obvious beads of dark, brown discolouration corresponding to the introduced water droplets. Suspension affected in this way should not be used as it may have significantly reduced potency.

Shake before use.

In case of the occurrence of allergic reaction, the treatment should be withdrawn.

Inappropriate use of the product may increase the prevalence of bacteria resistant to amoxicillin/clavulanic acid.

In animals with hepatic and renal failure the dosing regime should be carefully evaluated.

Caution is advised in the use of small herbivores other than those in 4.3.

Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies.

Narrow spectrum antibacterial therapy should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

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

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.

In case of contact with eyes, rinse immediately with plenty of water.

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.

4.6 Adverse reactions (frequency and seriousness)

Diarrhoea, vomiting and sweating may rarely occur after administration of the product.Use of the product may occasionally result in pain or itching on injection and / or local tissue reaction.

Hypersensitivity reactions unrelated to dose can occur with these agents. Allergic reactions (e.g., skin reactions, anaphylaxis) may occasionally occur.

Local tissue reactions at the site of injection may occur following administration. These reactions are generally of mild to moderate swelling and/or hardness and can persist for up to 2 weeks following administration at the recommended dose rate in the rump or leg muscles and 4 days after administration at the recommended dose rate in the neck muscles. Pain on injection may occasionally occur.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals have not produced any evidence of teratogenic effects. The safety of the product has not been assessed in pregnant and lactating cows or bitches.
Use only according to the benefit/risk assessment by the responsible veterinary surgeon.

4.8 Interaction with other medicinal products and other forms of interaction

The bactericidal effect of amoxicillin is neutralized by simultaneous use of bacteriostatic acting pharmaceuticals (macrolides, sulfonamides and tetracyclines).

The potential for allergic cross-reactivity with other penicillins should be considered. Penicillins may increase the effects of aminoglycosides.

4.9 Amounts to be administered and administration route

The product is indicated for intramuscular administration to cattle and subcutaneous administration to dogs.

The recommended dosage rate of 8.75 mg/kg bodyweight [7 mg/kg bodyweight amoxicillin and 1.75 mg/kg/bodyweight of clavulanic acid] (1 ml per 20 kg bodyweight) once daily for 3-5 days. Shake the vial well before use. Use a completely dry sterile needle and syringe. Swab the septum before removing each dose.

In Cattle, the maximum volume administered at the site of injection should not exceed 10 ml.

See also section 4.5 (i)

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

In Cattle, the product is well tolerated up to 2 times the recommended dose administered for up to 5 days.

Studies in cattle at the normal dose rate and twice the normal dose rate have shown transient and dose dependent muscle damage at the injection site resulting in increased Creatine kinase and Aspartate Aminotransferase levels. Injection site reactions tended to be dose dependent and were fully resolved by 2 weeks after administration to the leg and rump and 4 days after administration to the neck even at twice the recommended dose rate. No other clinically significant abnormalities were detected.

The product is well tolerated up to 3 times the recommended dose rate administered for up to 6 days for dogs however, in dogs, reactions at the injection site may occur at 3 times the recommended dose rate resolving after 2 weeks.

4.11 Withdrawal period

Meat and offal : 42 days.
Milk 60 hours [5 milkings]

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antimicrobial

ATC Vet Code: QJ01CR02

5.1 Pharmacodynamic properties

Mode of Action

Amoxicillin is a beta-lactam antibiotic and its structure contains the beta-lactam ring and thiazolidine ring common to all penicillins. Amoxicillin shows activity against susceptible Gram positive bacteria and Gram negative bacteria.

Beta-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. They inhibit the activity of transpeptidase enzymes, which catalyse cross-linkage of the glycopeptide polymer units that form the cell wall. They exert a bactericidal action but cause lysis of growing cells only.

Clavulanic acid is one of the naturally occurring metabolites of the streptomycete *Streptomyces clavuligerus* . It has structural similarity to the penicillin nucleus, including possession of a beta-lactam ring. Clavulanic acid is a beta-lactamase inhibitor acting initially competitively but ultimately irreversibly.

Clavulanic acid will penetrate the bacterial cell wall binding to both extracellular and intracellular beta-lactamases.

Amoxicillin is susceptible to breakdown by ß-lactamases produced by some bacterial species, and therefore combination with an effective ß-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include ß-lactamase producing species.

In vitro potentiated amoxicillin is active against a wide range of clinically important bacteria including *Pasteurella multocida* and *Mannheimia haemolytica.*

Another possible mode of resistance to beta-lactam antibiotics can be associated with chromosomal mutations in bacteria resulting in modification of the penicillin binding proteins (PBPs) or modification of the cellular permeability to β-lactam antibiotics by their nature such chromosomal mutations tend to be relatively slow in development primarily by vertical transmission. A trend in resistance of *E. coli* is reported.

No clinical breakpoints have been established by the CLSI for amoxicillin/clavulanic acid against the target pathogens in cattle.

In dogs, the following MIC breakpoints have been established for amoxicillin/clavulanic acid:

Pathogen	**MIC breakpoints (µg/ml)**			
		Susceptible	Intermediate	Resistant
Escherichia coli	Skin/soft tissue infections	≤ 0.25/0.12	0.5/0.25	≥ 1/0.5
	Urinary tract infections	≤ 8/4		
Staphylococcus spp.	Skin/soft tissue infections	≤ 0.25/0.12	0.5/0.25	≥ 1/0.5

	Urinary tract infections	≤ 8/4		

Source: CLSI document VET08 (2018)

5.2 Pharmacokinetic properties

After intramuscular administration to cattle and subcutaneous administration to dogs, amoxicillin and clavulanic acid are well absorbed and distributed in the tissues. The principle route of elimination of amoxicllina and clavulanic acid is in the urine.

After intramuscular administration of the product to cattle at the recommended dose once daily for five consecutive days, the following parameters were observed:

Cmax of 1.69 µg/ml, Tmax of 2.67h, AUC of 30.59 µg/ml.h and t½ of 15.22h for amoxicillin and Cmax of 0.94 µg/ml, Tmax of 1.3h, AUC of 3.123 µg/ml.h and t½ of 1.71h for clavulanic acid.

After subcutaneous administration of the maximum recommended dose to dogs, the following parameters were observed: Cmax of 8.66 µg/ml, Tmax of 1.78 h and AUC of 50.98 µg/ml.h for amoxicillin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol Dicaprylate/Dicaprate
Butylated hydroxyanisole
Butylated hydroxytoluene

6.2 Incompatibilities

Do not mix with other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 1 year
Shelf-life after first opening the immediate packaging: 28 days

6.4 Special precautions for storage

Do not store above 25ºC.
Once a vial has been broached the contents should be used within 28 days.
Discard unused material.

6.5 Nature and composition of immediate packaging

The product will be supplied in clear colourless type II glass vials of 50 ml and 100 ml, complete with nitryl bungs and aluminium caps.

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

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

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

(UK)
Norbrook Laboratories Limited
Station Works
Camlough Road
Newry
Co. Down
BT35 6JP
Northern Ireland

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

13 January 2003

10. DATE OF REVISION OF THE TEXT

December 2019

CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synuclav Suspension for Injection (UK)
Clavobay Suspension Injectable (FR)
Noroclav Suspension for Injection (PT)
Noroclav 175 mg Suspension for Injection (ES)
Noroclav Injection (BE, IT)
Combisyn Injection (IS)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Synuclav Injection is an off-white suspension containing amoxicillin 140 mg/ml as amoxicillin trihydrate and clavulanic acid 35 mg/ml as potassium clavulanate in an oily base.
Excipients: Butylated hydroxyanisole (E320) 0.08mg and Butylated hydroxytoluene (E321) 0.08mg.

3. PHARMACEUTICAL FORM

Suspension for Injection

4. PACKAGE SIZE

50 /100 ml

5. TARGET SPECIES

Cattle and Dogs

6. INDICATION(S)

In cattle:

- Treatment of Mastitis
- Treatment of respiratory infections due to *Pasteurella multocida* and *Mannheimia haemolytica.*

In dogs:
Respiratory tract infections, urinary tract infections, skin and soft tissue infections (e.g. abscesses, pyoderma, anal sacculitis and gingivitis).

7. METHOD AND ROUTE(S) OF ADMINISTRATION

The product is indicated for intramuscular administration to cattle and subcutaneous administration to dogs.

The recommended dosage rate of 8.75 mg/kg bodyweight [7mg/kg bodyweight amoxicillin and 1.75 mg/kg/bodyweight of clavulanic acid] (1 ml per 20 kg bodyweight) once daily for 3-5 days.

Shake before use. Use a completely dry sterile needle and syringe. Swab the septum before removing each dose. The suspension is not suitable for intravenous or intrathecal administration.
In Cattle, the maximum volume administered at the site of injection should not exceed 10ml.

8. WITHDRAWAL PERIOD

Meat and offal: 42 days
Milk: 60 hours [5 milkings]

9. SPECIAL WARNING(S), IF NECESSARY

Do not use in animals with known hypersensitivity to penicillin or other substances of the beta-lactam group. Do not use in rabbits, guinea pigs, hamsters or gerbils. Do not use in animals with serious dysfunction of kidneys accompanied by anuria or oliguria. The use of the product is contra-indicated where resistance to the combination of penicillins or other substances of the beta-lactam group is known to occur.

Diarrhoea, vomiting and sweating may rarely occur after administration of the product. Local tissue reactions at the site of injection may occur following administration. These reactions are generally of mild to moderate swelling and/or hardness and can persist for up to 2 weeks following administration at the recommended dose rate in the rump or leg muscles and 4 days after administration at the recommended dose rate in the neck muscles. Pain on injection may occasionally occur.

In case of the occurrence of allergic reaction, the treatment should be withdrawn. Inappropriate use of the product may increase the prevalence of bacteria resistant to amoxicillin/clavulanic acid. In animals with hepatic and renal failure the dosing regime should be carefully evaluated. Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies. Narrow spectrum antibacterial therapy should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

The safety of the product has not been assessed in pregnant and lactating cows or bitches.

User Warnings:
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.
In case of contact with eyes, rinse immediately with plenty of water.
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.

10. EXPIRY DATE

EXP: DD/MM/YY

11. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Once a vial has been broached the contents should be used within 28 days. Discard unused material.

Clavulanic acid is moisture sensitive. It is very important, therefore, that a completely dry syringe is used when extracting suspension for injection to avoid contaminating the remaining contents of the vial with water.

Contamination will result in distinct beads of dark, brown discolouration corresponding to the introduced water droplets. Material affected in this way should not be used as it may have significantly reduced potency.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

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

For animal treatment only.

<Supply category to be completed nationally>

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

Keep out of the reach and sight 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
Northern Ireland

16. MARKETING AUTHORISATION NUMBER

17. MANUFACTURER'S BATCH NUMBER

D.O.M.
B.N.:

FURTHER INFORMATION
Amoxicillin is a beta-lactam antibiotic and its structure contains the beta-lactam ring and thiazolidine ring common to all penicillins. Amoxicillin shows activity against susceptible Gram positive and Gram negative bacteria.

Beta-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. They inhibit the activity of transpeptidase enzymes which catalyse cross-linkage of the glycopeptide polymer units that form the cell wall. They exert a bactericidal action but cause lysis of growing cells only.

Clavulanic acid is one of the naturally occurring metabolites of the streptomycete *Streptomyces clavuligerus*. It has a structural similarity to the penicillin nucleus including possession of a beta-lactam ring. Clavulanic acid is a beta-lactamase inhibitor acting initially competitively but ultimately irreversibly.

Clavulanic acid will penetrate the bacterial cell wall binding to both extracellular and intracellular beta-lactamases.

Amoxicillin is susceptible to breakdown by β-lactamases produced by some bacterial species, and therefore combinations with an effective β-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include β-lactamase producing species.

Another possible mode of action of resistance to beta-lactam antibiotics can be associated with chromosomal mutations in bacteria resulting in modifications of the penicillin binding proteins (PBPs) or modification of the cellular permeability to β-lactam antibiotics by their nature such chromosomal mutations tend to be relatively slow in development primarily by vertical transmission. A trend in resistance of *E. coli* is reported.

The potential for allergic cross-reactivity with other penicillins should be considered. Penicillins may increase the effects of aminoglycosides.

LOGO

DRAFT LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synuclav Suspension for Injection (UK)
Clavobay Suspension Injectable (FR)
Noroclav Suspension for Injection (PT)
Noroclav 175 mg Suspension for Injection (ES)
Noroclav Injection (BE, IT)
Combisyn Injection (IS)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Suspension containing amoxicillin 140 mg/ml as amoxicillin trihydrate and clavulanic acid 35 mg/ml as potassium clavulanate in an oily base.

3. PHARMACEUTICAL FORM

Suspension for injection

4. PACKAGE SIZE

50/100 ml

5. TARGET SPECIES

Cattle and Dogs

6. INDICATION(S)

See package leaflet

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Cattle: By intramuscular injection at a dosage rate of 8.75 mg/kg bodyweight (equivalent to 1 ml per 20 kg bodyweight) daily for 3 to 5 days).
Dogs: By subcutaneous injection at a dosage rate of 8.75 mg/kg bodyweight (equivalent to 1 ml per 20 kg bodyweight) daily for 3 to 5 days.
Shake the vial well before use. Use a completely dry needle and syringe. Swab the septum before removing each dose. After injection massage the injection site.

8. WITHDRAWAL PERIOD

Meat & Offal: 42 days
Milk: 60 hours [5 milkings]

9. SPECIAL WARNING(S), IF NECESSARY

Do not use in rabbits, guinea pigs, hamsters or gerbils. Do not use in animals with serious dysfunction of kidneys accompanied by anuria or oliguria.
User warnings

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

10. EXPIRY DATE

EXP: DD/MM/YY

11. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC. Once a vial has been broached the contents should be used within 28 days. Discard unused material.

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

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

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

FOR ANIMAL TREATMENT ONLY.

<Supply category to be completed nationally>

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

Keep out of the reach and sight 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
Camlough Road
Newry
Co. Down
BT35 6JP
Northern Ireland

16. MARKETING AUTHORISATION NUMBER

17. MANUFACTURER'S BATCH NUMBER

B.N.:
DOM:

Once broached use by (dd/mm): ___/___

PACKAGE LEAFLET

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

Marketing Authorisation Holder
(EU)
Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
Ireland

(UK)
Norbrook Laboratories Limited
Station Works
Newry
Co. Down, BT35 6JP
Northern Ireland

Manufacturer Responsible for Batch Release

Norbrook Manufacturing Ltd.,
Rossmore Industrial Estate
Monaghan
Ireland

Norbrook Laboratories Limited
Station Works
Newry
Co. Down, BT35 6JP
Northern Ireland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synuclav Suspension for Injection (UK)
Clavobay Suspension Injectable (FR)
Noroclav Suspension for Injection (PT)
Noroclav 175 mg Suspension for Injection (ES)
Noroclav Injection (BE, IT)
Combisyn Injection (IS)

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

Synuclav Injection is an off-white suspension containing amoxicillin 140 mg/ml as amoxicillin trihydrate and clavulanic acid 35 mg/ml as potassium clavulanate in an oily base.
Excipients: Butylated hydroxyanisole 0.08mg and Butylated hydroxytoluene 0.08mg.

4. INDICATION(S)

In cattle:

- Treatment of Mastitis
- Treatment of respiratory infections due to *Pasteurella multocida* and *Mannheimia haemolytica.*

In dogs:
Respiratory tract infections, urinary tract infections, skin and soft tissue infections (e.g. abscesses, pyoderma, anal sacculitis and gingivitis).

5. CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to penicillin or other substances of the beta-lactam group. Do not use in rabbits, guinea pigs, hamsters or gerbils. Do not use in animals with serious dysfunction of kidneys accompanied by anuria or oliguria. The use of the product is contra-indicated where resistance to the combination of penicillins or other substances of the beta-lactam group is known to occur.

6. ADVERSE REACTIONS

Diarrhoea, vomiting and sweating may rarely occur after administration of the product. Hypersensitivity reactions unrelated to dose can occur with these agents. Allergic reactions (e.g., skin reactions, anaphylaxis) may occasionally occur.
Local tissue reactions at the site of injection may occur following administration. These reactions are generally of mild to moderate swelling and/or hardness and can persist for up to 2 weeks following administration at the recommended dose rate in the rump or leg muscles and 4 days after administration at the recommended dose rate in the neck muscles. Pain on injection may occasionally occur.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle and Dogs

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

The product is indicated for intramuscular administration to cattle and subcutaneous administration to dogs.

The recommended dosage rate of 8.75 mg/kg bodyweight [7mg/kg bodyweight amoxicillin and 1.75 mg/kg/bodyweight of clavulanic acid] (1 ml per 20 kg bodyweight) once daily for 3-5 days.

9. ADVICE ON CORRECT ADMINISTRATION

Shake before use. Use a completely dry sterile needle and syringe. Swab the septum before removing each dose. The suspension is not suitable for intravenous or intrathecal administration.
In Cattle, the maximum volume administered at the site of injection should not exceed 10ml.

The product is well tolerated up to 2 times the recommended dose administered for up to 5 days in Cattle.

Studies in cattle at the normal dose rate and twice the normal dose rate have shown transient and dose dependent muscle damage at the injection site resulting in increased Creatine kinase and Aspartate Aminotransferase levels. Injection site reactions tended to be dose dependent and were fully resolved by 2 weeks after administration to the leg and rump and 4 days after administration to the neck even at twice the recommended dose rate. No other clinically significant abnormalities were detected.

In Dogs, subcutaneous administration of 3 times the recommended dose can induce a reaction at the injection site that can persist up to 2 weeks after the injection.

The product is well tolerated up to 3 times the recommended dose administered for up to 6 days for Dogs.

Do not mix with other veterinary medicinal products.

10. WITHDRAWAL PERIOD

Meat & Offal: 42 days
Milk: 60 hours [5 milkings]

11. SPECIAL STORAGE PRECAUTIONS

Do not store above 25ºC.
Store out of the reach and sight of children.
Once a vial has been broached the contents should be used within 28 days.
When the container is broached (opened) for the first time, the date on which any product remaining in the container should be discarded should be calculated. A statement of the in use shelf life of the product is given on the package. This discard date should be written in the space provided on the label. Discard unused material.

Clavulanic acid is moisture sensitive. It is very important, therefore, that a completely dry syringe is used when extracting suspension for injection to avoid contaminating the remaining contents of the vial with water.

Contamination will result in distinct beads of dark, brown discolouration corresponding to the introduced water droplets. Material affected in this way should not be used as it may have significantly reduced potency.

12. SPECIAL WARNINGS

Precautions for use in Animals

This product does not contain an antimicrobial preservative.

In case of the occurrence of allergic reaction, the treatment should be withdrawn. Inappropriate use of the product may increase the prevalence of bacteria resistant to amoxycillin/clavulanic acid and to other substances of the beta-lactam group. In animals with hepatic and renal failure the dosing regime should be carefully evaluated. Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies. Narrow spectrum antibacterial therapy should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Caution is advised in the use in small herbivores other than those in section 5.

Studies in laboratory animals have not produced any evidence of teratogenic effects. The safety of the product has not been assessed in pregnant and lactating cows or bitches.

Use only according to a risk benefit assessment by the responsible veterinary surgeon.

User Warnings:

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.
In case of accidental contact with eyes, rinse immediately with plenty of water.
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.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

PACKAGE QUANTITIES:
50 ml / 100 ml multidose vials.

FURTHER INFORMATION

Amoxicillin is a beta-lactam antibiotic and its structure contains the beta-lactam ring and thiazolidine ring common to all penicillins. Amoxicillin shows activity against susceptible Gram positive and Gram negative bacteria.

Beta-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stages of peptidoglycan synthesis. They inhibit the activity of transpeptidase enzymes which catalyse cross-linkage of the glycopeptide polymer units that form the cell wall. They exert a bactericidal action but cause lysis of growing cells only.

Clavulanic acid is one of the naturally occurring metabolites of the streptomycete *Streptomyces clavuligerus*. It has a structural similarity to the penicillin nucleus including possession of a beta-lactamase inhibitor acting initially competitively but ultimately irreversibly.

Clavulanic acid will penetrate the bacterial cell wall binding to both extracellular and intracellular beta-lactamases.

Amoxicillin is susceptible to breakdown by β-lactamases produced by some bacterial species, and therefore combination with an effective β-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include β-lactamase producing species.

Another possible mode of resistance to beta-lactam antibiotics can be associated with chromosomal mutations in bacteria resulting in modification of the penicillin binding proteins (PBPs) or modification of the cellular permeability to β-lactam antibiotics by their nature such chromosomal mutations tend to be relatively slow in development primarily by vertical transmission. A trend in resistance of *E. coli* is reported.

The bactericidal effect of amoxicillin is neutralized by simultaneous use of bacteriostatic acting pharmaceuticals (macrolides, sulfonamides and tetracyclines).
The potential for allergic cross-reactivity with other penicillins should be considered.
Penicillins may increase the effects of aminoglycosides.

MARKETING AUTHORISATION NUMBER

DISTRIBUTED BY:

<Supply category to be completed nationally>

LOGO