SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nisinject Suspension for Injection (Belgium, Italy, UK)
Nisinject 175mg Suspension for Injection (Portugal, Spain)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml 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:
Mastitis
Respiratory infections
Soft tissue infections (e.g. joint/navel ill, abscesses etc.)

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 contra-indicated 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

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.

4.5 Special precautions for use

i. Special 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In case of the occurrence of allergic reaction, the treatment should be withdrawn.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 dosage regime should be carefully evaluated.

Use of the product should be based on susceptibility testing and taking 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 4.3.

ii. Special precautions to be taken by the person administering the veterinary medicinal products 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 accidental 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. 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. Use of the product may occasionally result in pain or itching on injection and / or local tissue reaction.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals have not produced any evidence of teratogenic effects. Use only according to the benefit/risk assessment by the responsible veterinary surgeon.

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

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 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.

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 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 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 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 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:

Gram positive:

Staphylococci (including beta-lactamase producing strains)
Streptococci
Corynebacterium
Clostridia

Gram negative:

Escherichia coli
Campylobacter spp
Klebsiella spp
Proteus spp

Pasteurella spp
Bacteroides (including beta-lactamase producing strains)
Haemophilus spp.

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.

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 amoxicillin and clavulanic acid is in the urine.

After intramuscular administration of the product 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 15.22 hr 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 1.78h 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

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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 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
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Northern Ireland

8. MARKETING AUTHORISATION NUMBER

9. DATE OF RENEWAL OF AUTHORISATION

Date: 28 April 2009

10. DATE OF REVISION OF THE TEXT

Date: