SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nisamox 50 mg Tablets for dogs and cats (in all CMS and RMS ES, IT, NL, UK.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per tablet:

Active Ingredients:

Amoxicillin (as amoxicillin trihydrate)	40 mg
Clavulanic acid (as Potassium clavulanate)	10 mg

Excipients:

Carmoisine Lake (E122)	0.245mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.
Round pink tablet with a score line and 50 embossed on opposing faces.

4. CLINICAL PARTICULARS

4.1 Target Species

Dogs and cats.

4.2 Indications for Use, Specifying the Target Species

Treatment of the following infections caused by β lactamase producing strains of bacteria sensitive to amoxicillin in combination with clavulanic acid:

- Skin infections (including superficial and deep pyodermas) caused by susceptible Staphylococci.
- Urinary tract infections caused by susceptible Staphylococci or *Escherichia coli*.
- Respiratory infections caused by susceptible Staphylococci.
- Enteritis caused by susceptible *Escherichia coli*.

It is recommended to carry out suitable tests for sensitivity testing when initiating the treatment. The treatment should only proceed if sensitivity is proven to the combination.

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 rabbits, guinea pigs, hamsters or gerbils.
Do not use in animals with serious dysfunction of the kidneys accompanied by anuria and oliguria.
Do not use where resistance to this combination is known to occur.
Do not administer to horses and ruminating animals.

4.4 Special Warnings for Each Target Species

None.

4.5 Special Precautions for Use

i. Special precautions for use in animals

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 regimen 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 likely efficacy of this approach.
Caution is advised in the use in small herbivores other than those in 4.3.
Dogs and cats diagnosed with *Pseudomonas* infections should not be treated with this antibiotic combination.

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.

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)

Hypersensitivity reactions unrelated to dose can occur with these agents.
Gastrointestinal symptoms (diarrhoea, vomiting) may occur after administration of the product.
Allergic reactions (e.g. skin reactions, anaphylaxia) may occasionally occur.
In case of occurrence of allergic reaction, the treatment should be withdrawn.

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 veterinarian.

4.8 Interaction with other Medicinal Products and Other Forms of Interaction

Chloramphenicol, macrolides, sulfonamides and tetracyclines may inhibit the antibacterial effect of penicillins because of the rapid onset of bacteriostatic action. The potential for allergic cross-reactivity with other penicillins should be considered.
Penicillins may increase the effect of aminoglycosides.

4.9 Amounts to be Administered and Administration

Administration is via the oral route. The dosage rate is 12.5 mg combined actives/kg bodyweight twice daily. The tablets may be crushed and added to a little food.

The following table is intended as a guide to dispensing the product at the standard dose rate of 12.5 mg of combined actives per kg twice daily.

Bodyweight	Number of tablets twice daily
1-2	½
3-4	1
5-6	1,5
7-8	2
9-10	2,5
11-12	3
13-14	3,5
15-16	4
17-18	4,5

Duration of therapy
Acute cases: 5 to 7 days of treatment.
If no improvement is observed after 5 to 7 days, the diagnosis should be re-assessed.

Chronic or refractory cases: In these cases where there is considerable tissue damage, a longer course of therapy may be required so that it allows sufficient time for damaged tissue to repair.
If no improvement is observed after two weeks, the diagnosis should be re-assessed.

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

The product is of a low order of toxicity and is well tolerated by the oral route.

In a tolerance study in dogs a tested dose of 3 times the recommended dose of 12.5mg of the combined actives administered twice daily for 8 days did not demonstrate adverse effects.

In a tolerance study in cats a tested dose of 3 times the recommended dose of 12.5mg of the combined actives administered twice daily for 15 days did not demonstrate adverse effects.

4.11 Withdrawal Period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Beta-lactam antibacterials, penicillins

ATCvet code: QJ01CR02

5.1 Pharmacodynamic properties

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 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-lactamase and therefore combination with an effective ß-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include β-lactamase producing species.

In vitro potentiated amoxicillin is active against a wide range of clinically important aerobic and anaerobic bacteria including:

Gram-positive:
Staphylococci (including β-lactamase producing strains)
Clostridia
Streptococci

Gram-negative:
Escherichia coli (including most β-lactamase producing strains)
Campylobacter spp
Pasteurellae
Proteus spp

Resistance is shown among *Enterobacter* spp, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. A trend in resistance of *E. coli* is reported.

5.2 Pharmacokinetic properties

Amoxicillin is well-absorbed following oral administration. In dogs the systemic bioavailability is 60-70%. Amoxicillin (pKa 2.8) has a relatively small apparent distribution volume, a low plasma protein binding (34% in dogs) and a short terminal half-life due to active tubular excretion via the kidneys. Following absorption the highest concentrations are found in the kidneys (urine) and the bile and then in liver, lungs, heart and spleen. The distribution of amoxicillin to the cerebrospinal fluid is low unless the meninges are inflamed.

Clavulanic acid (pK1 2.7) is also well-absorbed following oral administration. The penetration to the cerebrospinal fluid is poor. The plasma protein binding is approximately 25% and the elimination half-life is short. Clavulanic acid is heavily eliminated by renal excretion (unchanged in urine).

After oral administration of the recommended dose of 12.5mg combined actives/kg to dogs, the following parameters were observed: Cmax of 6.30 +/- 0.45µg/ml, Tmax of 1.98 +/- 0.135h and AUC of 23.38 +/- 1.39 µg/ml.h for amoxicillin and Cmax of 0.87 +/- 0.1µg/ml, Tmax of 1.57 +/- 0.177hrs and AUC of 1.56 +/- 0.24mg/ml.h for clavulanic acid.

After oral administration of the recommended dose of 12.5mg combined actives/kg to cats, the following parameters were observed: Cmax of 7.12 +/- 1.460 µg/ml, Tmax of 2.69 +/- 0.561 h and AUC of 33.54 +/- 7.335 µg/ml.h for

amoxicillin and Cmax of 1.67 +/- 0.381 µg/ml, Tmax of 1.83 +/- 0.227 h and AUC of 7.03 +/- 1.493 µg/ml.h for clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipient(s)

Carmosine Lake (E122)
Sodium Starch Glycollate
Copovidone
Magnesium Stearate
Microcrystalline Cellulose
Calcium Carbonate
Silicon Dioxide
Heavy Magnesium carbonate
Roast Beef Flav-o-lok

6.2 Major incompatibilities

Not applicable.

6.3 Shelf-Life

Shelf-life of the veterinary medicinal product as packaged for sale:
Blister packs: 2 years
Tubs: 6 months

6.4 Special Precautions for Storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and Composition of Immediate Packaging

The product is supplied in high-density polyethylene tubs with a polypropylene screw cap lid containing 100 tablets and in high-density polyethylene tubs with a polyethylene screw cap lid containing 500 tablets. A sachet of desiccant is included in each container. The product is also presented in packs containing 2, 10 and 50 blister strips (aluminium-aluminium) each containing 10 tablets per strip.

Not all pack sizes may be marketed.

6.6 Special Precautions for the Disposal of Unused Veterinary Medicinal Products or Waste Materials Derived From the Use of Such Products, if appropriate

Any unused product or waste material should be disposed of in accordance with national requirements.

7. NAME OR CORPORATE NAME AND ADDRESS OR REGISTERED PLACE OF BUSINESS OF THE MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date: 3rd January 2003 / 25th February 2009

10. DATE OF REVISION OF THE TEXT

Date: