PRODUCT SUMMARY

1. Name of the Veterinary Medicinal Product
MULTIBIO

2. Qualitative and Quantitative Composition
Each ml contains:

- **Active Ingredients**:
    - Ampicillin ..... 100 mg (anhydrous)
    - Colistin sulfate ..... 250,000 IU
    - Dexamethasone acetate ..... 0.25 mg
- **Excipients**:
    - Benzyl Alcohol ..... 0.009 ml
    - For the full list of excipients, refer to section 6.1.

3. Pharmaceutical Form
Injection Suspension

4. Clinical Characteristics
4.1. Target Species
Cattle

4.2. Indications for Each Target Species
Multibio is used for the treatment of acute mastitis caused by bacterial species such as *Staphylococcus spp.*, *Streptococcus spp.*, *Enterobacter*, *Escherichia coli* in lactating cows, and for the treatment of the following bacterial infections in cattle associated with ampicillin and colistin-sensitive bacterial strains:

- Respiratory tract infection caused by *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida*
- Digestive system disease caused by *Escherichia coli*, *Salmonella spp.*
- Genitourinary tract infection caused by *Escherichia coli*, *Pasteurella spp.*, *Pseudomonas spp.*, *Fusobacterium spp.*
- Septicemia caused by *Escherichia coli*.

4.3. Contraindications
Not to be used in animals with hypersensitivity to penicillin and cephalosporins. Not for use in rabbits, guinea pigs, hamsters, or animals with split hooves.

4.4. Special Warnings for Each Target Species

As with all penicillins, this product may cause hypersensitivity (allergic) reactions after administration. It should be used cautiously if there is hypersensitivity to ampicillin, colistin, or any excipients. Although normally non-irritant, it may sometimes cause local reactions at the injection site.

4.5. Special Precautions for Use

i) **Special precautions for use in animals**:

The product should be used based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, treatment should be based on local (regional, farm-level) epidemiological information about the sensitivity of the target bacteria.
Colistin is a last-resort drug used for treating infections caused by various multidrug-resistant bacteria. To minimize potential risks associated with the wide use of colistin, its use should be restricted to the instructions provided in this summary.

The treatment should not be used if there is resistance to both ampicillin and colistin.
Careful adherence to the label instructions is required to avoid underdosing, which can lead to treatment failure and potentially increase bacterial resistance prevalence.
Ensure the correct body weight of the animal is determined to avoid underdosing.

ii) Precautions for the user and veterinarian:

Persons known to be hypersensitive to ampicillin, colistin, or any excipients should avoid contact with this veterinary medicinal product.
Penicillin sensitivity may lead to cross-sensitivity with cephalosporins, and vice versa. Allergic reactions to these substances are rarely serious.
If you are known to be sensitive to these compounds, or if you have been advised to avoid them, do not handle this product.

In case of eye contact, rinse thoroughly with water.
If symptoms such as skin redness develop after exposure to the product, seek medical advice and show the product packaging to the doctor. Swelling of the face, lips, or eyes and difficulty breathing are more severe symptoms and require urgent medical attention.

4.6. Adverse Reactions (Frequency and Severity)

Animals should be monitored for corticosteroid-induced immunosuppression after treatment.
Polymyxins have strong unwanted effects on kidneys and nerves. Their kidney effects are increased by aminoglycosides and certain cephalosporins (such as cephaloridine). Parenteral administration of polymyxins can cause balance disorders, loss of sensation in the head, arms, and legs, and muscle weakness.
Colistin has a tendency to accumulate in tissues after high-dose administration and can cause kidney failure. Colistin also has a fetotoxic effect.

In animals sensitive to penicillin, hypersensitivity reactions such as urticaria, fever, and angioneurotic edema may occur. Rarely, acute anaphylaxis and collapse can occur. If intolerance symptoms are observed, stop treatment and administer symptomatic and supportive treatment (epinephrine and/or oxygen, glucocorticoids) if necessary.

Also, when dexamethasone is used in late pregnancy, it may cause labor to start.

4.7. Use During Pregnancy and Lactation

The safety of this product during pregnancy in the target species has not been evaluated. It should not be used in pregnant or lactating animals.
In laboratory animals, parenteral administration of colistin has shown fetotoxic effects. Corticosteroids, when used in pregnant mammals, can inhibit development and, if used in late pregnancy, may induce labor or cause miscarriage.

4.8. Interactions with Other Medicinal Products and Other Forms of Interaction

Bacteria that show cross-resistance to other ß-lactam antibiotics, particularly gram-negative organisms, may develop resistance to ampicillin.
There is antagonism between ampicillin and other bacteriostatic antibiotics.
There may be specific interactions between colistin sulfate and anesthetics or muscle relaxants following oral administration. Avoid using colistin sulfate with aminoglycosides and levamisole. The effects of colistin sulfate are antagonized by divalent cations (iron, calcium, magnesium) and unsaturated fatty acids and polyphosphates. There is cross-resistance between colistin and polymyxin B.
Corticosteroids can reduce immune responses to vaccinations, so dexamethasone-containing products should not be used alongside vaccines.
This product should not be used with bacteriostatic molecules such as sulfonamides, tetracyclines, and macrolides. The nephrotoxic potential of aminoglycosides (such as streptomycin, neomycin, and gentamicin) and cephalosporins is increased when used in combination with colistin, although the risk is minimal.

As a result, because MULTIBIO contains two broad-spectrum antibiotics and a glucocorticoid, it should not be used together with other veterinary medicinal products.

4.9. Dosage and Administration Route

Unless otherwise recommended by the veterinarian, MULTIBIO is administered intramuscularly:

- **Pharmacological dose**: 10 mg ampicillin, 25,000 IU colistin, and 0.025 mg dexamethasone per kg body weight
- **Practical dose**: 1 ml (0.1 g ampicillin, 250,000 IU colistin, and 0.25 mg dexamethasone) per 10 kg body weight, administered intramuscularly once a day for 3-5 days.

Practical dosage table is as follows:

Weight (kg)	The amount of Multibio to be administered	Route of administration	Duration of administration
10 kg	1 ml	Intramuscular(IM)	3-5 days
100 kg	10 ml	Intramuscular(IM)	3-5 days
500 kg	50 ml	Intramuscular(IM)	3-5 days

4.10. Overdose, Symptoms, Emergency Procedures, and Antidotes
Administration of up to five times the recommended dose in cattle did not result in any signs of intolerance.

4.11. Withdrawal Period
The withdrawal period for this veterinary medicinal product (meat and milk) is as follows:

- **Meat**: Cattle should not be sent for slaughter until 42 days after the last administration of the product.
- **Milk**: Milk from treated cows should not be sold for human consumption within 5 days (120 hours) after the last administration of the product.

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5. Pharmacological Properties

Pharmacotherapeutic Group: Systemic use anti-infectives – combinations of antibiotics and other components – antibiotics and corticosteroids
ATCvet Code: QJ01RV01

5.1. Pharmacodynamic Properties

Multibio combines ampicillin and colistin antibiotics with dexamethasone, a steroid-based anti-inflammatory drug.

- **Ampicillin**
    - **Mode of Action**: Ampicillin is a broad-spectrum penicillin that has a time-dependent bactericidal effect through inhibition of bacterial cell wall synthesis. It is effective against both Gram-positive and Gram-negative bacteria.
    - **Resistance Mechanism**: There are two main resistance mechanisms. First, bacteria can produce β-lactamase (penicillinase or cephalosporinase), which deactivates the antibiotic. This enzyme is common in both Gram-positive and Gram-negative bacteria. Second, the affinity of ampicillin for penicillin-binding proteins (PBPs) can be altered. These mechanisms are common in Gram-positive bacteria (e.g.,

Staphylococcus aureus, *Streptococcus pneumoniae*, *Enterococcus faecium*) but are less frequent in Gram-negative bacteria. Drug efflux pumps can also contribute to resistance. These mechanisms can coexist in the same organism and lead to cross-resistance with other β-lactams and antimicrobial drug classes.

- **Susceptibility**: Ampicillin is particularly effective against Gram-positive and Gram-negative bacteria but is also susceptible to β-lactamase enzymes.
- **Clinical Data**: In cattle, the MIC50 for key respiratory pathogens such as *Histophilus somni*, *Mannheimia haemolytica*, and *Pasteurella multocida* ranges from ≤0.03 µg/mL to 0.25 µg/mL. A clinical study on lactating cows with acute mastitis found that 71.5% of coagulase-negative *Staphylococcus* strains and 100% of coagulase-positive strains were sensitive to ampicillin. Other species such as *Streptococcus agalactiae* and *Streptococcus dysgalactiae* were also sensitive.

- **Colistin**
  - **Mode of Action**: Colistin is a narrow-spectrum polymyxin antibiotic with concentration-dependent bactericidal activity against many Gram-negative aerobic bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter spp.*, and *Salmonella spp.* It disrupts the cytoplasmic membrane, altering cell permeability.
  - **Resistance Mechanism**: Colistin is effective primarily against Gram-negative bacteria, and resistant organisms typically possess cell walls that prevent colistin from entering. Cross-resistance with polymyxin B has been reported, but no cross-resistance between colistin and other classes of antibiotics has been detected to date.
  - **Susceptibility**: In cattle, the MIC50 for *E. coli* and *Salmonella spp.* are 0.25 and 1 µg/mL, respectively. A clinical study on lactating cows with acute mastitis showed that 75% of *Enterobacter* strains and 100% of *E. coli* strains were sensitive to colistin.

- **Dexamethasone**
  - Dexamethasone is a synthetic glucocorticoid with potent anti-inflammatory effects and minimal mineralocorticoid activity. Glucocorticoids can reduce immune responses by inhibiting capillary dilation, leukocyte migration, and phagocytosis. Dexamethasone is used

in this combination to reduce inflammation associated with bacterial infections.

5.2. Pharmacokinetic Properties

- **Ampicillin**:
  Following intramuscular injection, ampicillin is absorbed rapidly and completely, with over 80% bioavailability. Peak plasma concentrations (approximately 8-18 ng/mL) are reached within 2 hours. It is widely distributed in tissues, with approximately 20% of it weakly bound to plasma proteins. The elimination half-life is short due to renal tubular excretion, and elimination occurs mainly through bile and urine within 2-4 hours.
- **Colistin**:
  Following intramuscular injection, colistin sulfate is rapidly absorbed and widely distributed. Peak plasma concentrations are reached within 0.5-2 hours. Its elimination half-life does not exceed 5-6 hours, and it is primarily eliminated unchanged by the kidneys. Colistin has low milk excretion, with a small portion eliminated through bile and the milk ducts.
- **Dexamethasone**:
  Dexamethasone is rapidly and almost completely absorbed after intramuscular injection. Peak plasma concentrations are reached within 30 minutes, and its elimination half-life ranges between 5 and 20 hours, depending on the species. Dexamethasone is widely distributed to tissues, interstitial fluid, brain, and cerebrospinal fluid. The bioavailability following intramuscular application is approximately 100%, and it is primarily excreted via urine and milk.

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6. Pharmaceutical Particulars

6.1. List of Excipients

- Benzyl alcohol
- Butylhydroxyanisole
- Polyoxyl 35 castor oil
- Propylene glycol dicaprylate/dicaprate

6.2. Incompatibilities

None known.

6.3. Shelf Life

When stored under the recommended conditions, the shelf life is 24 months from the manufacturing date. After first use, the product remains effective for 28 days when kept

in its original packaging at room temperature. The stopper puncture count should not exceed 28.

6.4. Storage Conditions
Store in the original packaging at room temperature (15–25°C). Do not store in a refrigerator or freezer.

6.5. Nature and Composition of the Primary Packaging
The product is supplied in multidose Type II transparent glass vials with aluminum caps and brown-red rubber stoppers, available in 50 mL, 100 mL, and 250 mL sizes, packed in cartons.

6.6. Special Disposal Instructions for Used or Leftover Product
Unused veterinary medicinal products or waste materials should be disposed of in accordance with national regulations. Do not dispose of these products in wastewater or drainage systems.

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7. Marketing Authorization Holder

Virbac Animal Health Ltd.
Zekeriyaköy Mah. Kilyos Cad. No: 272 A6/D5 Sarıyer 34450 Istanbul, TURKEY

8. Marketing Authorization Number: 10/032

9. Date of Marketing Authorization, Updates, and Renewals

- **First Authorization Date**: 13/12/2005
- **Last Update/ Renewal Date**: 26/08/2019

10. Last Revision Date: 26/08/2019