Composition

Curacef Duo Injectable Suspension is a sterile, white to pinkish suspension containing 51.5 mg of ceftiofur hydrochloride (equivalent to 50 mg of ceftiofur) and 150 mg of ketoprofen per 1 ml.

Pharmacological Properties

Pharmacodynamic Properties

Ceftiofur is a third-generation cephalosporin effective against a wide range of gram-positive and gram-negative bacteria. Like other beta-lactams, ceftiofur exerts its bactericidal action by inhibiting bacterial cell wall synthesis.

Cell wall synthesis depends on enzymes called penicillin-binding proteins (PBPs). Bacteria can develop resistance to cephalosporins through four main mechanisms:

1. Modification or acquisition of penicillin-binding proteins that have reduced sensitivity to beta-lactams with different activity.
2. Changes in the permeability of the cell membrane to beta-lactams.
3. Production of beta-lactamases that break the beta-lactam ring of the molecule.
4. Active efflux-mediated elimination.

Some beta-lactamases found in gram-negative enteric organisms can lead to increased Minimum Inhibitory Concentration (MIC) levels for third- and fourth-generation cephalosporins, as well as penicillins, ampicillin, beta-lactam inhibitor combinations, and first- and second-generation cephalosporins.

Ceftiofur is effective against the following microorganisms that cause respiratory diseases in cattle: *Pasteurella multocida* and *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*).

MICs for ceftiofur were detected in European bacterial isolates from diseased animals between 2009 and 2012.

Species (Number of Isolates)	MIC Range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)
Mannheimia haemolytica (91)	0.002-4	0.015	0.06
Pasteurella multocida (155)	0.008-0.25	0.015	0.03

MIC Profiles of Target Respiratory Pathogens

The MICs for target respiratory pathogens exhibit a highly sensitive single-modal distribution profile against ceftiofur. Clinical breakpoints for ceftiofur against

Mannheimia haemolytica and *Pasteurella multocida* in cattle respiratory diseases have been defined (CLSI Vet 01-52 guidelines):

- Sensitive: ≤2 µg/ml
- Intermediate: 4 µg/ml
- Resistant: ≥8 µg/ml

According to these breakpoints, no clinically resistant strains of target respiratory pathogens have been observed.

Ketoprofen
Ketoprofen is a derivative of phenylpropionic acid and belongs to the non-steroidal anti-inflammatory drug (NSAID) class.
Its mechanism of action is related to ketoprofen's ability to inhibit prostaglandin synthesis from precursors like arachidonic acid. Following endotoxin production, although ketoprofen does not have a direct effect on endotoxins, it reduces prostaglandin production, thereby diminishing their effects. Prostaglandins play a role in the complex processes leading to endotoxemic shock. Like all molecules in this therapeutic class, its primary pharmacological effects are anti-inflammatory, analgesic, and antipyretic.

Pharmacokinetic Properties
After administration, ceftiofur is rapidly metabolized into its active metabolite, desfuroylceftiofur. Desfuroylceftiofur has antimicrobial activity equivalent to ceftiofur against target bacteria in animals. The active metabolite is reversibly bound to plasma proteins. Due to its transport by these proteins, the metabolite concentrates at the infection site, maintaining its activity even in the presence of necrotic tissue and tissue debris.

Ceftiofur is fully bioavailable after intramuscular administration. After a single dose of 1 mg ceftiofur (hydrochloride)/kg body weight in cattle, the maximum plasma concentration (Cmax) of ceftiofur and desfuroylceftiofur metabolites reaches 6.11 ± 1.56 µg/ml within 5 hours (Tmax). The half-life (t½) for plasma concentration reduction of ceftiofur and its metabolites is 19 hours. Elimination is predominantly via urine (more than 55%), with about 31% of the dose found in the feces.

Ketoprofen is also fully bioavailable after intramuscular administration. After a single dose of 3 mg ketoprofen/kg body weight, the maximum plasma concentration (Cmax) of ketoprofen reaches 5.55 ± 1.58 µg/ml within 4 hours (Tmax). The half-life (t½) for ketoprofen plasma concentration reduction is 3.75 hours. Ketoprofen has a high protein binding rate in cattle (97%). Elimination primarily occurs via urine (90% of the dose), metabolized into metabolites.

Indications for Use
In cattle:
Indicated for the treatment of respiratory diseases (BRD) caused by *Mannheimia haemolytica* and *Pasteurella multocida*, and for the reduction of clinical signs associated with inflammation or fever.

Dosage and Administration
Administer via intramuscular injection.

- 1 mg of ceftiofur/kg body weight/day and 3 mg ketoprofen/kg body weight/day, equivalent to 1 ml suspension per 50 kg of body weight.
  The product should only be used when associated with disease, inflammation, or fever.
  The product can be administered for 1 to 5 days depending on clinical response. As antibiotic treatment should last for at least 3-5 days, when inflammation and fever subside, the veterinarian should transition to a ceftiofur-only treatment for 3 to 5 additional days. Only a small number of animals are expected to require a fourth or fifth injection with the combination product.

Shake the bottle for 20 seconds to homogenize the suspension before use. If stored at low temperatures, this may take a longer time. Accurate body weight assessment of animals is crucial to prevent underdosing.

For large-scale treatment, use the most appropriate presentation for the number of animals. The 50 ml and 100 ml bottles should not be punctured more than 10 times, while the 250 ml bottle should not be punctured more than 18 times. To prevent damage to the cap, the use of an aspiration needle is recommended.

Do not administer successive injections to the same site. Do not exceed 16 ml per injection site.

Special Clinical Information and Target Species-Specific Warnings
Due to the potential risk of renal toxicity, avoid use in dehydrated, hypovolemic, or hypotensive animals. Treatment should be discontinued in case of allergic reactions. CURACEF DUO may select for resistant strains, such as those carrying extended-spectrum beta-lactamases (ESBL), which can pose a risk to human health if transmitted through contaminated food. Therefore, CURACEF DUO should be used for treating clinically serious cases that have failed initial empirical therapy or are likely to fail. After the reduction of inflammation or fever, the veterinarian should switch to ceftiofur-only

therapy for a continuous 3 to 5-day course of antibiotics. Adequate treatment duration is essential to limit resistance development.

The simultaneous use of diuretics or coagulants should be based on a benefit-risk assessment by the responsible veterinarian.
Official, national, and regional antimicrobial policies should be considered when using the product. Inappropriate or excessive use, including off-label use, can increase the prevalence of resistance.

CURACEF DUO should be used based on sensitivity testing whenever possible. It is a veterinary medicine intended for individual animal treatment. It should not be used for disease prevention or as part of established health programs. Group treatment should be strictly limited to ongoing disease outbreaks in accordance with approved usage conditions.

Avoid subcutaneous and intravenous administration. Preferably, use a 14-gauge needle. Good animal husbandry practices should be followed in animal housing, care, feeding, treatment, and in the establishment and operation of livestock businesses to prevent disease occurrence.

Use During Pregnancy, Lactation, and Egg Laying
Although laboratory animal studies with seftiofur and ketoprofen have not shown teratogenicity, abortion, or effects on reproduction, the reproductive safety of this product in pregnant cows has not been specifically studied. It should only be used based on a benefit-risk assessment by a responsible veterinarian.

Undesirable Effects
In field studies, CURACEF DUO was tested in cattle ranging from 1 month to 12 years of age without safety concerns. In most cases, mild inflammatory reactions, such as painless tissue edema at the injection site, were commonly observed. Non-dose-dependent hypersensitivity reactions (e.g., skin reactions, anaphylaxis) and discoloration in subcutaneous tissue and/or muscle may rarely occur.
Like all NSAIDs, very rare gastric or renal intolerance may be observed due to the inhibition of prostaglandin synthesis.

Frequency of Adverse Effects

- Very common: Affects more than one animal in every 10 animals treated.
- Common: Affects more than 1 but fewer than 10 animals in every 100 treated.
- Uncommon: Affects more than 1 but fewer than 10 animals in every 1,000 treated.

- Rare: Affects more than 1 but fewer than 10 animals in every 10,000 treated.
- Very rare: Affects fewer than 1 animal in every 10,000 animals treated.

Drug Interactions
Some NSAIDs may excessively bind to plasma proteins and compete with other drugs that are also highly protein-bound, potentially leading to toxic effects.
Do not use with other NSAIDs, corticosteroids, diuretics, nephrotoxic drugs, or anticoagulants.

The bactericidal activity of beta-lactams can be impaired by concurrent use with bacteriostatic antibiotics (macrolides, sulfonamides, and tetracyclines).

Overdose Symptoms, Measures, and Antidote
No systemic toxicity symptoms have been observed after administering doses up to 5 times the recommended daily dose for 15 consecutive days.

Contraindications
Do not use in animals known to be hypersensitive to other cephalosporins, beta-lactams, or ketoprofen.
Do not use in humans due to the risk of antimicrobial resistance in poultry (including eggs).

Contraindications
This product should not be used in cases of known resistance to other cephalosporins or beta-lactam antibiotics. If resistance is observed, a different antimicrobial from a different class should be used.
It should not be used in combination with other non-steroidal anti-inflammatory drugs (NSAIDs) within 24 hours.
This product is contraindicated in animals with evidence of blood dyscrasias, gastrointestinal ulceration or bleeding, and in animals with cardiac, hepatic, or renal diseases.

Residue Warnings for Food-Producing Animals
Drug Withdrawal Time (DWT):

- Cattle destined for meat and edible offal must not be slaughtered for 8 days after the last dose.
- Milk withdrawal time for cows is 0 days.

General Warnings

Read the prospectus before use. Consult a veterinarian if any unexpected effects occur. Store in a place out of reach of children and away from food products. Do not buy or use products with damaged packaging.

Precautions for Handlers and Medical Personnel

Penicillins and cephalosporins may cause hypersensitivity (allergic) reactions after injection, inhalation, ingestion, or skin contact. Hypersensitivity to penicillins may lead to cross-reactivity with cephalosporins or vice versa. Additionally, ketoprofen may cause hypersensitivity reactions. Allergic reactions to these substances can occasionally be severe.

If you are known to be hypersensitive to any of the active or excipient ingredients, or have been advised not to work with such products, do not use this product.

Wash your hands after use. Avoid contact with eyes and skin. In case of contact, rinse immediately with water. Swelling of the face, lips, or eyes, or difficulty in breathing, are serious symptoms requiring urgent medical attention. In case of accidental self-injection, seek immediate medical help and show the prospectus or label to the doctor.

Disposal Instructions for Unused Product and Non-target Species

Unused portions of this veterinary medicinal product or waste from such veterinary medicinal products should be disposed of according to regional requirements.

Storage Conditions and Shelf Life

Store in the original packaging at temperatures below 25°C. The shelf life is 3 years from the manufacturing date.

Do not store in a refrigerator or freeze.

Store the glass bottle protected from light in its outer packaging. Once opened, it remains effective for 28 days when stored in its original packaging at 25°C.

It is recommended that the stopper be punctured no more than 10 times for 50 ml and 100 ml vials and no more than 18 times for 250 ml vials.

Commercial Presentation

The product is presented in a carton box containing a 50, 100, or 250 ml amber-colored glass vial with a gray rubber (bromobutyl) stopper and aluminum cap.

Sales Information and Conditions
This product is available for sale through veterinary prescription in pharmacies, veterinary clinics, polyclinics, and hospitals (VHR).

Prospectus Approval Date: 04.04.2023
Ministry of Agriculture and Forestry of Turkey Marketing Authorization Date and No: 04.04.2023-015/0095

Marketing Authorization Holder and Address
Virbac Animal Health Limited Company
Levent Mah. Cömert Sok. No:1 Yapı Kredi Plaza C Block, Floor 17, No:40, Levent-Beşiktaş, Istanbul

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Manufacturer Company and Address
VIRBAC, 1ere Avenue M-LID 06516 Carros - France