

For Veterinary Use Only

ACTIONIS

Injectable Suspension

Veterinary Systemic Antibacterial

COMPOSITION White or yellowish-white Injectable Suspension contains 50 mg/ml ceftiofur (as hydrochloride).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Ceftiofur is a 3rd generation cephalosporin and is effective against most Gram-positive and Gram-negative bacteria. Ceftiofur acts by inhibiting bacterial cell wall synthesis. Beta-lactams act by interfering with bacterial cell wall synthesis. Cell wall synthesis depends on enzymes called penicillin-binding proteins. Bacteria develop resistance to cephalosporins through 4 main mechanisms; 1) By making penicillin-binding proteins insensitive, 2) By altering the beta-lactam permeability of the cell wall, 3) By producing beta-lactamases that enable the cleavage of the beta-lactam ring, 4) Active efflux. Some beta-lactamases found in Gram-negative enteric organisms can variably increase the MIC values of first and second generation cephalosporins, beta-lactam inhibitory combinations, penicillins, ampicillins, and third and fourth generation cephalosporins.

The MIC values for target bacteria obtained from infected animals in Europe are as follows: For ceftiofur, the Clinical and Laboratory Institute has recommended the following values for respiratory pathogens listed on the label.

Bacteria (number of isolates)	MIC range (µg/mL)	MIC₉₀ (µg/mL)
<i>Mannheimia haemolytica</i> (149)	≤ 0.002 - 0.12	0.015
<i>Pasteurella multocida</i> (134)	≤ 0.002 - 0.015	0.004
<i>Histophilus somni</i> (66)	≤ 0.002 - 0.008	0.004
<i>Truiperella pyogenes</i> (35)	0.25 - 4	2
<i>Escherichia coli</i> (209)	0.13 - 2	0.5
<i>Fusobacterium necrophorum</i> (67)(Foot rot isolates)	≤ 0.06 - 0.13	TE
<i>Fusobacterium necrophorum</i> (2)(akut metrit isolates)	≤ 0.03 - 0.06	TE

TE: could not be detected.

Zone (mm)	MIC ($\mu\text{g/mL}$)	Evaluation
≥ 21	≤ 2.0	(S) Susceptible
18 - 20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

Pharmacokinetic properties After administration, ceftiofur is rapidly metabolized to its primary metabolite, desfuroylceftiofur. This metabolite has antimicrobial activity equal to ceftiofur. It binds reversibly to plasma proteins. Due to this protein binding, the metabolite is actively present at the site of infection and remains active in the presence of pus and necrotic tissue. In cattle, after a single subcutaneous administration at a dose of 1 mg/kg, the maximum plasma level ($2.85 \pm 1.11 \mu\text{g/mL}$) was reached two hours after administration. In healthy cattle, in a single application, the C_{max} level in the endometrium was measured as $2.25 \pm 0.79 \mu\text{g/mL}$ after 5 ± 2 hours. Maximum concentrations in the caruncle and lochia were measured as $1.11 \pm 0.24 \mu\text{g/mL}$ and $0.98 \pm 0.25 \mu\text{g/mL}$, respectively. The half-life in cattle is 11.5 ± 2.57 hours. No accumulation was observed in daily treatments lasting longer than five days. Excretion occurs primarily via urine (more than 55%) and feces (31%). Bioavailability of ceftiofur after subcutaneous administration is complete.

INDICATIONS In cattle, for the treatment of infections caused by ceftiofur-susceptible strains:

- Treatment of respiratory system infections caused by strains of *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*), *Pasteurella multocida*, and *Histophilus somni* (formerly *Haemophilus somnus*),
- Treatment of acute interdigital necrobacillosis (panaritium, foot rot) caused by *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*),
- Treatment of acute post-partum (puerperal) metritis caused by *Escherichia coli*, *Arcanobacterium pyogenes*, and *Fusobacterium necrophorum* within 10 days after calving, where treatment with other antibiotics has failed.

DOSAGE AND ADMINISTRATION Before use, shake the vial vigorously for no more than 60 seconds or until sufficiently suspended. To ensure correct dosage, the body weights of the animals should be measured as accurately as possible. No more than 7 ml should

be injected into one injection site. Injections on different days should be made at different sites. **Respiratory system infections:** 1 mg/kg body weight daily for 3-5 days subcutaneously (1 ml of product per 50 kg body weight daily). **Acute interdigital necrobacillosis:** 1 mg/kg body weight daily for 3 days subcutaneously (1 ml of product per 50 kg body weight daily). **Acute post-partum metritis (within 10 days after calving):** 1 mg/kg body weight daily for 5 days subcutaneously (1 ml of product per 50 kg body weight daily). In this infection, supportive treatment may be required in some cases.

SPECIAL CLINICAL INFORMATION AND SPECIAL WARNINGS FOR TARGET SPECIES

Shake the vial well to revert to suspension before use. Treatment should be discontinued if allergic reactions are observed. This product is selective for resistant strains producing extended-spectrum beta-lactamases, which may pose a risk to human health (e.g., via food). For this reason, this product should be reserved for cases where initial treatment has yielded or is expected to yield poor results (severe acute conditions where treatment must be initiated without bacteriological diagnosis). Regional and national antimicrobial policies should be taken into account when using this product. Increased use of this product, including use different from that specified in this document, may lead to an increase in the prevalence of resistant bacteria. Therefore, the product should be used based on susceptibility test results whenever possible. It is not used for preventive purposes in case of retained placenta. This product is for individual treatment. It is not used as part of disease prevention or herd health programs. Group treatment of animals should be limited only to disease outbreaks in accordance with the approved conditions of use. **Use during pregnancy, lactation, and lay:** Although studies in laboratory animals have not shown effects on teratogenicity, abortion, or reproduction, the safe use of the product in pregnant cows has not been investigated. It should only be used during pregnancy according to the benefit/risk assessment of the Veterinarian.

ADVERSE EFFECTS Dose-independent hypersensitivity reactions may occur. Allergic reactions (such as skin reactions, anaphylaxis) have been reported very rarely (less than 1 in 10,000 animals). Swelling and hardness at the application site were observed after subcutaneous administration in cattle. Local tissue reactions (edema, discoloration, etc.) ranging from mild to moderate were observed up to 42 days after injection. According to field reports, injection site reactions are very rare.

DRUG INTERACTIONS The bactericidal effect of beta-lactams is inhibited by bacteriostatic antibiotics such as macrolides, sulfonamides, and tetracyclines. Aminoglycosides positively influence the effect of cephalosporins. Should not be mixed with other products.

SYMPTOMS OF OVERDOSE, PRECAUTIONS, AND ANTIDOTE No significant signs of systemic toxicity were observed in cases of parenteral overdose in cattle.

WITHDRAWAL PERIOD FOR FOOD-PRODUCING ANIMALS Cattle should not be slaughtered for human consumption for 8 days following the last treatment. The withdrawal period for milk is "0" (zero) days.

CONTRAINDICATIONS Do not use in animals known to be hypersensitive to ceftiofur or beta-lactams. Do not administer intravenously. Do not use in cases where resistance to other cephalosporins or beta-lactams has developed. Do not use in poultry, including layers, due to the risk of antimicrobial resistance to humans.

GENERAL WARNINGS Consult a Veterinarian before use and in case of an unexpected effect. Keep out of reach of children. Keep away from food items.

PRECAUTIONS TO BE TAKEN BY THE APPLICATOR AND ADVICE FOR PHYSICIANS Penicillins and cephalosporins may cause hypersensitivity (allergy) reactions following injection, inhalation, ingestion, or skin contact. Sensitivity to penicillins leads to sensitivity to cephalosporins (or vice versa). Rarely, these reactions can be very serious. If you are sensitive and have received medical advice not to work with such products, do not touch this product. If symptoms such as skin rash develop, seek medical treatment immediately and show this warning to the health professional. Take necessary precautions to avoid accidental self-injection. In such a case, consult a healthcare institution immediately. Symptoms such as swelling of the face, lips, or eyes, or difficulty breathing are very serious and require urgent medical treatment. Wash hands after use.

STORAGE CONDITIONS AND SHELF LIFE The product, including after first use, should be stored in its original packaging below 25 °C, protected from light, and without being placed in a refrigerator or freezer. Shelf life is 2 years from the date of manufacture. Shelf life after the primary packaging is opened: 28 days.

DISPOSAL AND WARNINGS FOR NON-TARGET SPECIES Used or remaining products and waste materials should be disposed of in accordance with relevant legislation.

COMMERCIAL PRESENTATION It is offered for sale in cardboard boxes in 100 ml and 250 ml polyethylene terephthalate (PET) vials with bromobutyl rubber stoppers and aluminum caps or flip-off aluminum caps.

PLACE AND CONDITIONS OF SALE Sold in pharmacies, veterinary clinics, outpatient clinics, and animal hospitals with a Veterinary Surgeon's prescription (VHR).

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