

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Actionis 50 mg/ml, suspension for injection for pigs and cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Ceftiofur (as ceftiofur hydrochloride) 50.0 mg/ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

White to pale yellow oily suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs and cattle.

4.2 Indications for use, specifying the target species

Infections associated with bacteria sensitive to ceftiofur:

In pigs:

-For the treatment of bacterial respiratory disease associated with *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Streptococcus suis*.

In cattle:

-For the treatment of bacterial respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

-For the treatment of acute interdigital necrobacillosis (panaritium, foot rot), associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*).

-For treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with *Escherichia coli*, *Arcanobacterium pyogenes* and *Fusobacterium necrophorum*, sensitive to ceftiofur. The indication is restricted to cases where treatment with another antimicrobial has failed.

4.3 Contraindications

Do not administer to an animal previously found to be hypersensitive to ceftiofur and other β -lactam antibiotics.

The product should not be used in case of known resistance to ceftiofur or other β -lactam antibiotics.

Do not inject intravenously.

Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

4.4 Special warnings for each target species

None known

4.5 Special precautions for use

i. Special precautions for use in animals

ACTIONIS selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) and may constitute a risk to human health *if these strains disseminate to humans e.g. via food*. For this reason, *ACTIONIS* should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of such resistance.

Whenever possible, *ACTIONIS* should only be used based on susceptibility testing.

ACTIONIS is intended for treatment of individual animals. Do not use for disease prevention or as a part of herd health programmes. Treatment of groups of animals should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

Do not use as prophylaxis in case of retained placenta.

Shake vigorously before use during 1 minute or until the complete resuspendability of the product.

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.

1. Handle this product with great care to avoid exposure taking all recommended precautions.
Wash hands after use.
2. Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
3. In case of accidental self-injection or following exposure, if you develop symptoms 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 in breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

Hypersensitivity reactions unrelated to dose can occur. Allergic reactions (e.g. skin reactions, anaphylaxia) may occasionally occur. In case of the occurrence of allergic reaction the treatment should be withdrawn.

In swine, mild reactions at the injection site, such as discoloration of the fascia or fat, have been observed in some animals for up to 20 days after injection.

In cattle, mild inflammatory reactions at the injection site, such as tissue oedema and discoloration of the subcutaneous tissue and/or fascial surface of the muscle may be observed. Clinical resolution is reached in most animals by 10 days after injection although slight tissue discoloration may persist for 28 days or more.

4.7 Use during pregnancy, lactation or lay

Laboratory studies have not produced any evidence of a teratogenic, foetotoxic or maternotoxic effects.

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.

Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

The bactericidal properties of cephalosporins are antagonized by simultaneous use of bacteriostatic antibiotics (macrolides, sulfonamides and tetracyclines).

4.9 Amounts to be administered and administration route

Pigs:

3 mg ceftiofur /kg bw/day for 3 days via intramuscular route, i.e. 1 ml/16 kg bw at each injection.

Cattle:

Respiratory disease: 1 mg ceftiofur /kg bw/day for 3 to 5 days by subcutaneous injection, i.e. 1 ml/50 kg bw at each injection.

Acute interdigital necrobacillosis: 1 mg/kg bw/day for 3 days by subcutaneous injection, i.e. 1 ml/50 kg bw at each injection.

Acute post-partum metritis within 10 days after calving: 1 mg/kg bw/day for 5 consecutive days by subcutaneous injection, i.e. 1 ml/50 kg bw at each injection.

In case of acute post-partum metritis, additional supportive therapy might be required in some cases.

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid under dosing.

Not more than 5 ml should be administered at any one intramuscular injection site in pigs or 7 ml at any one subcutaneous injection site in cattle. Subsequent injections must be given at different sites.

Shake vigorously before use during 1 minute or until the complete resuspendability of the product.

The user should select the most appropriate vial size.

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

The low toxicity of ceftiofur has been demonstrated in pigs using ceftiofur sodium at doses in excess of 8 times the recommended daily dose of ceftiofur intramuscularly administered for 15 consecutive days.

In cattle, no signs of systemic toxicity have been observed following substantial parenteral overdosages.

4.11 Withdrawal period(s)

Pigs:

Meat and offal: 6 days.

Cattle:

Meat and offal: 6 days.

Milk: zero hours.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials, third generation cephalosporins.

ATCvet code: QJ01DD90

5.1 Pharmacodynamic properties

Ceftiofur is a third generation cephalosporin, which is active against many Gram-positive and Gram-negative bacteria, including β -lactamase producing strains. Like all beta-lactam antibiotics, ceftiofur inhibits the bacterial cell wall synthesis, thereby exerting bactericidal properties.

Beta-lactams act by interfering with synthesis of the bacterial cell wall. Cell wall synthesis is dependent on enzymes that are called penicillin-binding proteins (PBP's). Bacteria develop resistance to cephalosporins by four basic mechanisms: 1) altering or acquiring penicillin binding proteins insensitive to an otherwise effective β -lactam; 2) altering the permeability of the cell to β -lactams; 3) producing β -lactamases that cleave the β -lactam ring of the molecule, or 4) active efflux.

Some β -lactamases, documented in Gram-negative enteric organisms, may confer elevated MICs to varying degrees to third and fourth generation cephalosporins, as well as penicillins, ampicillins, β -lactam inhibitor combinations, and first and second generation cephalosporins.

Ceftiofur is active against the following microorganisms which are involved in respiratory diseases in pigs: *Pasteurella multocida*, *Actinobacillus*

pleuropneumoniae and *Streptococcus suis*. *Bordetella bronchiseptica* is intrinsically non-susceptible to ceftiofur.

It is also active against bacteria involved in respiratory disease in cattle: *Pasteurella multocida*, *Mannheimia haemolytica*, *Histophilus somni*; bacteria involved in acute bovine foot rot (interdigital necrobacillosis) in cattle: *Fusobacterium necrophorum*, *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli*, *Arcanobacterium pyogenes* and *Fusobacterium necrophorum*.

The following Minimum Inhibitory Concentrations (MIC) have been determined for ceftiofur in European isolates of target bacteria, isolated from diseased animals:

PIGS		
Organism (number of isolates)	MIC range (µg/mL)	MIC ₉₀ (µg/mL)
<i>A. pleuropneumoniae</i> (28)	≤ 0.03*	≤ 0.03
<i>Pasteurella multocida</i> (37)	≤ 0.03 - 0.13	≤ 0.03
<i>Streptococcus suis</i> (495)	≤ 0.03 - 0.25	≤ 0.03
Cattle		
Organism (number of isolates)	MIC range (µg/mL)	MIC ₉₀ (µg/mL)
<i>Mannheimia spp.</i> (87)	≤ 0.03*	≤ 0.03
<i>P. multocida</i> (42)	≤ 0.03 - 0.12	≤ 0.03
<i>H. somni</i> (24)	≤ 0.03*	≤ 0.03
<i>Arcanobacterium pyogenes</i> (123)	≤ 0.03 - 0.5	0.25
<i>Escherichia coli</i> (188)	0.13 - > 32.0	0.5
<i>Fusobacterium necrophorum</i> (67) (isolates from cases of foot rot)	≤ 0.06 - 0.13	ND
<i>Fusobacterium necrophorum</i> (2) (isolates from cases of acute metritis)	≤ 0.03 - 0.06	ND

*No range; all isolates yielded the same value. ND: not determined.

The following breakpoints are recommended by NCCLS for bovine and porcine respiratory pathogens currently on the label for ACTIONIS:

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2.0	(S) Susceptible
18 - 20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

No breakpoints have been determined to date for the pathogens associated with foot rot or acute post-partum metritis in cows.

5.2 Pharmacokinetic particulars

After administration, ceftiofur is quickly metabolised to desfuroylceftiofur, the principal active metabolite.

Desfuroylceftiofur has an equivalent anti-microbial activity to ceftiofur against the bacteria involved in respiratory disease in animals. The active metabolite is reversibly bound to plasma proteins. Due to transportation with these proteins, the

metabolite concentrates at a site of infection, is active and remains active in the presence of necrotic tissue and debris.

In pigs given a single intramuscular dose of 3 mg/kg body weight (bw), maximum plasma concentrations of $11.8 \pm 1.67 \mu\text{g/mL}$ were reached after 1 hour; the terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur was 16.7 ± 2.3 hours. No accumulation of desfuroylceftiofur has been observed after a dose of 3 mg ceftiofur/kg bw/day administered daily over 3 days.

The elimination occurred mainly via the urine (more than 70 %). Average recoveries in faeces accounted for approximately 12-15 % of the drug.

Ceftiofur is completely bioavailable following intramuscular administration.

After a single 1 mg/kg dose given subcutaneously to cattle, maximum plasma levels of $2.85 \pm 1.11 \mu\text{g/mL}$ are reached within 2 hours after administration. In healthy cows, a C_{max} of $2.25 \pm 0.79 \mu\text{g/mL}$ was reached in the endometrium 5 ± 2 hours after a single administration. Maximum concentrations reached in caruncles and lochia of healthy cows were $1.11 \pm 0.24 \mu\text{g/mL}$ and $0.98 \pm 0.25 \mu\text{g/mL}$, respectively.

The terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur in cattle is 11.5 ± 2.57 hours. No accumulation was observed after a daily treatment over 5 days. The elimination occurred mainly via the urine (more than 55 %); 31 % of the dose was recovered in the faeces.

Ceftiofur is completely bioavailable following subcutaneous administration.

Environmental properties

--

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminum monostearate
Polysorbate 80
Triglycerides, medium-chain.

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Cardboard box with 1 type II colourless glass bottle containing 100 or 250 ml with a type I bromobutyl rubber stopper and aluminium cap.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios SYVA S.A.U.
Avda. Párroco Pablo Díez, 49-57
24010 León
Spain

8. MARKETING AUTHORISATION NUMBER

Vm 31592/4004

9. DATE OF FIRST AUTHORISATION

Date: 7 June 2011

10. DATE OF REVISION OF THE TEXT

Date: March 2012

PROHIBITION OF SALE, SUPPLY AND/OR USE

For animal treatment only – to be supplied only on veterinary prescription.
Use by a veterinary surgeon or under their direct responsibility.