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

Each ml contains:

Active substance:

Ceftiofur (as ceftiofur hydrochloride) 50.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Aluminium monostearate
Polysorbate 80
Triglycerides, medium Chains

White to pale yellow oily suspension.

3. CLINICAL INFORMATION

3.1 Target species

Pigs and cattle.

3.2 Indications for use for each the target species

Infections associated with bacteria sensitive to ceftiofur:

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

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 *Prevotella melaninogenica* (*Porphyromonas asaccharolytica*).

For treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with *Escherichia coli*, *Trueperella pyogenes* and

Fusobacterium necrophorum, sensitive to ceftiofur. The indication is restricted to cases where treatment with another antimicrobial has failed.

3.3 Contraindications

Do not use in cases of hypersensitivity to ceftiofur and other β-lactam antibiotics or to any of the excipients.
Do not use in cases of known resistance to ceftiofur or other beta-lactam antibiotics.
Do not inject intravenously.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in target species:

This product does not contain an antimicrobial preservative.

The product 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, the product 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, the product should only be used based on susceptibility testing.
The product is intended for treatment of individual animals. Do not use for disease prevention or as a part of heard 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 for 1 minute or until the complete resuspension of the product.

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 veterinary medicinal 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.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

If you develop symptoms following exposure such as 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.
Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Pigs and cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction[1] Allergic reaction (e.g. skin reactions, anaphylaxis)[2]

[1] Unrelated to dose.
[2] In this case, the treatment should be withdrawn.

Pigs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site reaction (e.g. discoloration of the fascia or fat)[1]

[1]Mild reactions, discoloration can persist in some animals for up to 20 days after injection.

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site reaction (e.g. as tissue oedema, discoloration[1])[2]

[1] Subcutaneous tissue and/or fascial surface of the muscle.
[2] Mild inflammatory reactions, clinical resolution is reached in most animals by 10 days after injection although slight tissue discoloration may persist for 28 days or more.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See also section 16 of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.
Use only according to the benefit/risk assessment by the responsible veterinarian.

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

3.8 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).
Aminoglycosides may have a potentiating effect on cephalosporins.

3.9 Administration routes and dosage

Intramuscular or subcutaneous use.

To ensure a correct dosage, body weight should be determined as accurately as possible. The use of suitably calibrated measuring equipment is recommended.

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.

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 for 1 minute or until the complete resuspension of the product.
The user should select the most appropriate vial size.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal period(s)

Cattle:
Meat and offal: 6 days.
Milk: zero hours.

Pigs:
Meat and offal: 6 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01DD90

4.2 Pharmacodynamics

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*, *Prevotella melaninogenica* (*Porphyromonas asaccharolytica*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli*, *Trueperella 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)**
Actinobacillus pleuropneumoniae (28)	≤ 0.03*	≤ 0.03
Pasteurella multocida (37)	≤ 0.03 - 0.13	≤ 0.03
Streptococcus suis (495)	≤ 0.03 - 0.25	≤ 0.03

Cattle		
Organism (number of isolates)	**MIC range (µg/mL)**	**MIC_{90} (µg/mL)**
Mannheimia spp. (87)	≤ 0.03*	≤ 0.03
Pasteurella multocida (42)	≤ 0.03 - 0.12	≤ 0.03
Histophilus somni (24)	≤ 0.03*	≤ 0.03
Trueperella pyogenes (123)	≤ 0.03 - 0.5	0.25
Escherichia coli (188)	0.13 - > 32.0	0.5
Fusobacterium necrophorum (67) (isolates from cases of foot rot)	≤ 0.06 - 0.13	ND
Fusobacterium necrophorum (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.

4.3 Pharmacokinetics

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 ± 1.67 µg/mL were reached after 1 hour; the terminal elimination half-life (t½) 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 ± 1.11 µg/mL are reached within 2 hours after administration. In healthy cows, a Cmax of 2.25 ± 0.79 µg/mL was reached in the endometrium 5 ± 2 hours after a single administration. Maximum concentrations reached in caruncles and lochiae of healthy cows were 1.11 ± 0.24 µg/mL and 0.98 ± 0.25 µg/mL, respectively.

The terminal elimination half-life (t½) 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 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.

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

Polyethylene terephthalate (PET) vial of 100ml or 250ml with a type I nitrile-chlorobutyl rubber stopper and flip-off cap.

Formats:
Cardboard box with 1 vial of 100ml.
Cardboard box with 1 vial of 250ml.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater <or household waste>.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. MARKETING AUTHORISATION HOLDER

Laboratorios Syva S.A.
C/ Marqués de la Ensenada, 16
28004 Madrid
Spain

7. MARKETING AUTHORISATION NUMBER

Vm 31592/3003

8. DATE OF FIRST AUTHORISATION/

07 June 2011

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

February 2024

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).