1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cevaxel-RTU 50 mg/ml, suspension for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Ceftiofur (as hydrochloride) 50 mg
Equivalent to 53.45 mg of ceftiofur hydrochloride

Excipients:

Qualitative composition of excipients and other constituents
Silica, colloidal anhydrous
Sorbitan oleate
Propylene glycol dicaprylocaprate

Oily beige suspension

3. CLINICAL INFORMATION

3.1 Target species

Cattle and pigs.

3.2 Indications for use for each target species

Infections associated with bacteria sensitive to ceftiofur.

Cattle:
For the treatment of bacterial respiratory disease associated with *Histophilus somni, Mannheimia haemolytica* and*Pasteurella multocida* .
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*, *Trueperella pyogenes* and *Fusobacterium necrophorum*: this indication is restricted to cases where treatment with another antimicrobial has failed.

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

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 intravenously.
Do not use where resistance to other cephalosporins or beta-lactam antibiotics has occured.
Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species
Do not use as prophylaxis in case of retained placenta.
This veterinary medicinal 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, this veterinary medicinal 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 veterinary medicinal product is used. Increased use, including use of the veterinary medicinal product deviating from the instructions given in the SPC, may increase the prevalence of such resistance. Whenever possible, this veterinary medicinal product should only be used based on susceptibility testing.

This veterinary medicinal 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.

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.
People with known hypersensitivity to ceftiofur should avoid contact with the veterinary medicinal product.
Handle this veterinary medicinal product with great care to avoid exposure. Wash hands after use.
If you develop symptoms following exposure, such as a skin rash seek medical advice immediately and show the package leaflet or the label to the physician.
Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment
Not applicable.

3.6 Adverse events

Cattle

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction[1], Allergic skin reaction[1], Anaphylaxis[1]
Rare (1 to 10 animals / 10,000 animals treated):	Injection site reaction[2] (e.g. inflammation, oedema, thickening[3], discoloration[4])

[1]In case of the occurrence of allergic reaction the treatment should be withdrawn.
[2]Clinical resolution is reached in most animals by 10 days after injection although slight tissue discoloration may persist for 28 days or more.
[3]Of connective tissue
[4]Of the subcutaneous tissue and/or fascial surface of the muscle

Pigs

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction[1], Allergic skin reaction[1], Anaphylaxis[1]
Undetermined frequency (cannot be estimated from the available data)	Injection site reaction [2] (e.g. discoloration[3])

[1]In case of the occurrence of allergic reaction the treatment should be withdrawn.
[2]Mild, observed in some animals for up to 20 days after injection.
[3]Of the fascia or fat.

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 the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Studies in laboratory animals have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. The safety of the veterinary medicinal product has not been established in sows or cows during pregnancy and lactation.
Use only according to a benefit-risk assessment by the responsible veterinarian.

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).

3.9 Administration routes and dosage

Cattle: Subcutaneous use
- Respiratory disease: 1 mg ceftiofur (as hydrochloride)/kg /day for 3 to 5 days, i.e. 1 ml/50 kg at each injection.
- Acute interdigital necrobacillosis: 1 mg ceftiofur (as hydrochloride)/kg /day for 3 days, i.e. 1 ml/50 kg at each injection.
- Acute post-partum metritis within 10 days after calving: 1 mg ceftiofur (as hydrochloride)/kg /day for 5 consecutive days, i.e. 1 ml/50 kg at each injection.
In case of acute post-partum metritis, additional supportive therapy might be required in some cases.

Pigs: Intramuscular use
3 mg ceftiofur (as hydrochloride)/kg /day for 3 days, i.e. 1 ml/16 kg at each injection.

Shake the bottle well before use to bring the veterinary medicinal product back into suspension.
To ensure a correct dosage, body weight should be determined as accurately as possible . Subsequent injections must be given at different sites.
As the vial cannot be broached more than 50 times, the user should choose the more 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

Not applicable.

3.12 Withdrawal periods

Cattle:
Meat and offal: 8 days.
Milk: zero hours.

Pigs:
Meat and offal: 5 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01DD90

4.2 Pharmacodynamics

Ceftiofur is a third generation of cephalosporin, which is active against many Gram-positive and Gram-negative bacteria, including ß –lactamase producing strains.
Ceftiofur inhibits the bacterial cell wall synthesis, thereby exerting its 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) by altering or acquiring penicillin binding proteins insensitive to an otherwise effective ß - lactam;
2) by altering the permeability of the cell to ß-lactams;
3) by producing b -lactamases that cleave the ß-lactam ring of the molecule, or
4) by active efflux.

Some ß-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, b - 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 in cattle against:

- bacteria involved in respiratory disease: *Pasteurella multocida*, *Mannheimia spp.*, *Histophilus somni*;
- bacteria involved in acute interdigital necrobacillosis (foot rot) : *Fusobacterium necrophorum*, *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*); and
- bacteria associated with acute post-partum (puerperal) metritis: *Escherichia coli*, *Trueperella pyogenes* and *Fusobacterium necrophorum*.

The following Minimum Inhibitory Concentrations (MIC) have been determined for ceftiofur in European isolates (France, United Kingdom, Netherlands, Denmark, Germany, Belgium, Italy, Czech Republic, Ireland, Poland and Spain) collected from diseased animals between 2000 to 2012:

Bacteria species	Origin	Year	Nb of strains	MIC of ceftiofur (mcg/mL)		
				Range	MIC_{50}	MIC_{90}
Pasteurella multocida	Cattle	2009 to 2012	149	≤0.002 – 0.12	0.015	0.015
	Pigs	2009 to 2012	152	≤0.002 – 0.06	0.04	0.04
Mannheimia haemolytica	Cattle	2009 to 2012	149	≤0.002 – 0.12	0.015	0.015
Histophilus somni	Cattle	2009 to 2012	66	≤0.002-0.008	≤0.002	0.004
Escherichia coli	Cattle	2005 – 2006	163	0.06 – 1	0.23	0.44
Trueperella pyogenes	Cattle	2007 – 2008	30	0.06 – 0.25	0.09	0.12
Fusobacterium necrophorum	Cattle	2000 to 2006	27	0.015 – 16	0.1	0.2
Actinobacillus pleuropneumoniae	Pigs	2009 to 2012	157	0.008-2	0.015	0.03
Streptococcus suis	Pigs	2009 to 2012	151	–0.06-16	0.12	0.5

The following ceftiofur breakpoints are used: ≤2 mcg/mL (Susceptible), 4 mcg/mL (Intermediate) and ≥ 8 mcg/mL (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 13.2 mcg/mL were reached after 2 hours; the terminal elimination half-life (t½) of desfuroylceftiofur was 16.4 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 2.82 mcg/mL are reached within 4 hours after administration. In other studies, on healthy cows, a Cmax of 2.25 mcg/mL was reached in the endometrium 5 hours after a single administration. Maximum concentrations reached in caruncles and lochiae of healthy cows were 1.11 mcg/mL and 0.98 mcg/mL, respectively.
The terminal elimination half-life (t½) of desfuroylceftiofur in cattle is 12.1 hours. No accumulation was observed after a daily treatment over 5 days. The elimination occurs mainly via the urine (more than 55 %) and the faeces (30%). 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: 3 years
Shelf-life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

5.4 Nature and composition of immediate packaging

Immediate packaging:
Translucent multi-layer plastic Polypropylene/Ethylene vinyl alcohol/Polypropylene (PP/EVOH/PP) vials.
Chlorobutyl rubber stopper with aluminium cap.

Pack size
Cardboard box containing one 100 ml vial
Cardboard box containing one 250 ml vial
Cardboard box containing one 50 ml vial

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 system applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

VPA10815/016/001

8. DATE OF FIRST AUTHORISATION

21/04/2011

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

24/04/2026

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).