1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CEFOKEL 50 mg/ml suspension for injection for pigs and cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Ceftiofur (as hydrochloride) 50.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Ethyl oleate

White to off-white, beige suspension.

3. CLINICAL INFORMATION

3.1 Target species

Pigs and cattle.

3.2 Indications for use for each 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* (previously *Haemophilus somnus*).

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 the active substance and other β-lactam antibiotics.
Do not inject intravenously.
Do not use in cases where resistance to other cephalosporins or β-lactam antibiotics has occurred.
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
The veterinary medicinal product does not contain any antimicrobial preservative.

The 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, the 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 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, the veterinary medicinal product should only be used based on susceptibility testing.
The veterinary medicinal product is intended for treatment of individual animals. Do not use for disease prevention or as a part of herd health programs. 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.

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, you should seek medical advice and show the doctor this warning.

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, pigs:

Very common (>1 animal / 10 animals treated):	Injection site reaction[1] Injection site inflammation[2]
Undetermined frequency (cannot be estimated from the available data)	Hypersensitivity reaction[3], Allergic reaction[4] (e.g. allergic skin reaction, anaphylaxis)

[1] In pigs, mild. Discoloration of the fascia or fat, have been observed in some animals for up to 20 days after injection.
[2] In cattle, mild. 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.
[3] can occur unrelated to the dose.
[4] in case of the occurrence of allergic reaction the treatment should be withdrawn.

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 the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy, lactation and fertility:
Laboratory studies in animals have not produced any evidence of teratogenesis, abortion or influence on reproduction, however the reproductive safety of the active substance has not been specifically investigated in pregnant sows or cows.

Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

The bactericidal properties of β-lactams are neutralised by simultaneous use of bacteriostatic antibiotics (macrolides, sulphonamides and tetracyclines).

3.9 Administration routes and dosage

Intramuscular **(i.m.)** and subcutaneous (**s.c.**) use

Pigs:
3 mg ceftiofur/kg body weight (bw)/day for 3 days via **i.m.** 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 **s.c.** injection, i.e. 1 ml/50 kg bw at each injection.
Acute interdigital necrobacillosis: 1 mg/kg bw/day for 3 days by **s.c**. 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 **s.c.** injection, i.e. 1 ml/50 kg bw at each injection.

Before use, shake the bottle vigorously for at least 30 seconds until the product appears adequately resuspended. Following shaking the bottle should be visually examined to ensure that the product is

brought back into suspension. The absence of settled material can be confirmed by inverting the vial and viewing the contents through the base of the vial.

The recommended maximum volume to be administered at a single injection site is 4 ml in pigs and 6 ml in cattle. Subsequent injections must be given at different sites.
The vial cannot be broached more than 66 times.

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

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

Pigs:
Meat and offal: 5 days.

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

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 β–lactamase producing strains (except strains producing some type of extended spectrum betalactamases).
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 MIC data below represents EU isolate datasets over a particular time period. As the situation can differ both geographically and time dependently, strains of some bacteria listed may show development towards higher MIC90 values and could produce extended spectrum beta-lactamases. It could in some cases have an impact on clinical response to the treatment. Therefore, recommendations listed in point 3.5 should be thoroughly followed.

Pigs

Organism (number of isolates)	MIC range (µg/ml)	MIC_{90} (µg/ml)
A. pleuropneumoniae (28)	≤ 0.03*	≤ 0.03
Pasteurella multocida (37)	≤ 0.03 - 0.13	≤ 0.03
Streptococcus suis (227)	0.002 - 8	0.25

Cattle

Organism (number of isolates)	MIC range (µg/ml)	MIC_{90} (µg/ml)
Mannheimia spp. (87)	≤ 0.03*	≤ 0.03
P.multocida (42)	≤ 0.03 - 0.12	≤ 0.03
H.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 CLSI for bovine and porcine respiratory pathogens currently on the label:

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 7.20 ± 0.52 µg/ml were reached after 2 hour; the terminal elimination half-life (t½) of desfuroylceftiofur was 14.1 ± 2.8 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 4.29 ± 0.73 µg/ml are reached within 2 hours after administration. In healthy cows, a C_{max} 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 15.7 ± 4.2 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: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Do not refrigerate or freeze.
Keep the vial in the outer carton in order to protect from light.

5.4 Nature and composition of immediate packaging

Colourless glass type I vial of 100 ml, closed with grey coated bromobutyl rubber stoppers and aluminium caps.
Vials are individually packed in a carton box.
One, six, ten or twelve vials are grouped as a clinical pack.
Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products 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. NAME OF THE MARKETING AUTHORISATION HOLDER

Kela n.v.,

7. MARKETING AUTHORISATION NUMBER(S)

VPA10981/015/001

8. DATE OF FIRST AUTHORISATION

14/06/2013

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

16/09/2025

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).