SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CEFTIOCYL Fluid 50 mg/ml, suspension for injection for pigs and cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substance(s):
Ceftiofur (as hydrochloride) ..... 50.0 mg

Excipient(s):
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Slightly yellow to slightly pink, milky suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, pigs

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*.

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

4.3 Contraindications

Do not inject intravenously.

Do not use in poultry (including eggs) due to the risk of spread of antimicrobial resistance to humans. Do not use in cases of hypersensitivity to ceftiofur, to any other β-lactam antibiotics, or to any of the excipients.
Do not use in cases of known resistance to ceftiofur or other β-lactam antibiotics.

4.4 Special warnings for each target species

None known.

4.5 Special precautions for use

Special precautions for use in animals
In case of the occurrence of allergic reaction the treatment should be withdrawn.
The product selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) which may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, this 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 more narrow spectrum antimicrobial 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 ceftiofur/beta lactam resistant bacteria. Whenever possible, the product should only be used based on susceptibility testing.
Do not use as prophylaxis in case of retained placenta.
The 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 limited 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.
Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
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.
Wash hands after use.

Avoid contact with eyes and skin. In case of contact, wash immediately with plenty water.

4.6 Adverse reactions (frequency and seriousness)

Hypersensitivity reactions unrelated to dose can occur. Allergic reactions (e.g. skin reactions, anaphylaxis) may occasionally occur.

In pigs, 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 to moderate inflammatory reactions were observed following SC injection, presenting as firmness and swelling at the injection site. Chronic inflammation at these sites was observed in most animals until 42 days post-injection.
Discoloration of the subcutaneous tissue and/or fascial surface of the muscle at the injection site may be observed. Slight tissue discoloration may persist for 28 days or more.

4.7 Use during pregnancy, lactation or lay

The safety of the product has not been established in sows or cows during pregnancy or lactation. Studies in laboratory species have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. Use only according to a 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, sulphonamides and tetracyclines).

4.9 Amounts to be administered and administration route

For intramuscular (pigs) or subcutaneous (cattle) route.
To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.
Before use, shake the bottle vigorously for a maximum of 60 seconds or until the product appears adequately resuspended.
Pigs:
3 mg ceftiofur /kg bw/day for 3 days via intramuscular route, i.e. 1 ml/16 kg bw at each injection. Not more than 4 ml should be administered per injection site.
Subsequent injections must be given at different sites.
Cattle:
Respiratory disease: 1 mg ceftiofur /kg bw/day for 3 to 5 days by subcutaneous injection, i.e. 1 ml/50kg bw at each injection.
Acute interdigital necrobacillosis: 1 mg/kg bw/day for 3 days by subcutaneous injection, i.e. 1 ml/50kg 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.
Not more than 13 ml should be administered per injection site.
Subsequent injections must be given at different sites.
The closures must not be broached more than 30 times. Otherwise, the use of a multiple-dose syringe is recommended.
In case of acute post-partum metritis, additional supportive therapy might be required in some cases.

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: 2 days.
Cattle: meat and offal: 6 days; milk: zero hours.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, 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. 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*; and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli, Trueperella pyogenes* (former *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)**	**MIC90 (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
Haemophilus parasuis (16)	≤ 0.03 - 0.13	≤ 0.03
Cattle		
Organism (number of isolates)	**MIC range (µg/mL)**	**MIC90 (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 CLSI for bovine and porcine respiratory pathogens.

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), mean maximum plasma concentrations of desfuroylceftiofur corresponded to 11.7 µg/mL and were reached after 1.5 hours; the mean terminal elimination half-life (t½) of

desfuroylceftiofur was 12.25 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, mean maximum plasma levels of desfuroylceftiofur corresponded to 3.7 µg/mL and were reached within 3.0 hours after administration. In healthy cows, a Cmax of 2.25 µg/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 µg/mL and 0.98 µg/mL, respectively.
The mean terminal elimination half-life (t½) of desfuroylceftiofur in cattle is 9.79 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Water for injections
- Polysorbate 80
- Triglycerides medium-chain

6.2 Major incompatibilities

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

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

Do not store above 30°C. Store the vial upright.

6.5 Nature and composition of immediate packaging

Dark brown transparent type I glass vial with grey bromobutyl rubber stopper and sealed with aluminium cap, with flip-off.
Pack sizes:
Box with 1 vial of 50 ml
Box with 1 vial of 100 ml Box with 1 vial of 250 ml
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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vetoquinol UK Limited
Steadings Barn
Pury Hill Business Park
Nr Alderton
Towcester
Northamptonshire
NN12 7LS

8. MARKETING AUTHORISATION NUMBER

Vm 08007/4146

9. DATE OF FIRST AUTHORISATION

06 December 2017

10. DATE OF REVISION OF THE TEXT

September 2018

Approved: 11 September 2018