Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Cefenil RTU, 50 mg/ml, Suspension for Injection for Pigs and Cattle

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Ceftiofur (as hydrochloride) 50 mg

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

3 PHARMACEUTICAL FORM

Suspension for injection.
A white to yellowish coloured 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 *Porphyromonas asaccharolytica* (previously *Bacteroides melaninogenicus**)***.
For treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with *Trueperella pyogenes (*previously *Arcanobacterium pyogenes*) and *Fusobacterium necrophorum*. The indication is restricted to cases where treatment with another antimicrobial has failed.

4.3 Contraindications

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

4.4 Special warnings for each target species

None known

4.5 Special precautions for use

Special precautions for use in animals

This product selects for resistant strains such as bacteria carrying extended spectrum β-lactamases (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.

This product 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.

Special precautions to be taken by the person administering the medicinal products 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. Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.

2. Handle this product with great care to avoid exposure, taking all recommended precautions.
3. 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.

4.6 Adverse reactions (frequency and seriousness)

In cattle, mild inflammatory reactions such as hardness at the injection site have been observed in some animals. Clinical resolution is reached in most animals by 21 days after injection.

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

Hypersensitivity reactions unrelated to dose can occur. Allergic reactions (e.g. skin reactions, anaphylaxis) may occasionally occur. If an allergic reaction occurs, the treatment should be withdrawn.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory species have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects or of abortion. Safety of the product has not been investigated in the target species during pregnancy. Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

The bactericidal properties of β-lactams are neutralised by simultaneous use of bacteriostatic antibiotics (macrolides, sulphonamides 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. Subsequent injections must be given at different sites.
In case of acute post-partum metritis, additional supportive therapy might be required in some cases.

Before use, shake the bottle vigorously until the product appears adequately resuspended. The colour of the glass vial may not be uniform making it difficult to determine when the product is in suspension. Following shaking the absence of sediment can be confirmed most readily by inverting the vial and viewing the contents through the base of the vial.

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

The recommended maximum volume to be administered at a single injection site is 10 ml.
50 ml and 100 ml vials can only be broached a maximum of 50 times. 250 ml vials can only be broached a maximum of 85 times.

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)

Cattle:
Meat and offal: 5 days.
Milk: zero hours.

Pigs:
Meat and offal: 5 days.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, third generation cephalosporins
ATC vet code: QJ01D D90

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. Ceftiofur inhibits the bacterial cell wall synthesis, thereby exerting time dependent bactericidal properties

β-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 b -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 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, ß-lactam inhibitor combinations, and first and second generation cephalosporins.

Ceftiofur is active against the following micro-organisms which are involved in respiratory diseases in pigs: *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Streptococcus suis*.

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*, *Porphyromonas asaccharolytica* (previously *Bacteroides melaninogenicus*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Trueperella pyogenes* (previously *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)**
Actinobacillus pleuropneumoniae (157)	0.008 - 2	0.03
Pasteurella multocida (152)	≤ 0.002 - 0.06	0.004
Streptococcus suis (151)	0.06 - ≥16	0.5
Cattle		
Organism (number of isolates)	**MIC range (µg/mL)**	**MIC_{90} (µg/mL)**
Mannheimia haemolytica (149)	≤ 0.002 - 0.12	0.015
Pasteurella multocida (134)	≤ 0.002 - 0.015	0.004
Histophilus somni (66)	≤ 0.002 - 0.008	0.004
Truperella pyogenes (35) (previously	0.25 - 4	2

Arcanobacterium pyogenes		
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.

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 ± 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitan oleate
Aluminium Monostearate
Medium Chain Triglycerides

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: Glass: 2 years, Plastic: 2 years
Shelf-life after first opening of the immediate packaging: 28 days

6.4 Special precautions for storage

Do not store above 25° C.
Keep the vial in the outer carton in order to protect from light

6.5 Nature and composition of immediate packaging

50 ml, 100mL and 250mL type I clear glass vials or high density polyethylene (HDPE) vials
Each vial is closed with a nitryl bung and sealed with an aluminium cap. 100mL and 250mL type I clear glass vials are presented in a protective plastic sleeve in order to minimise breakage
Not all pack sizes may be marketed

6.6 Special precautions for the disposal of unused veterinary medicinal products 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

Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA22664/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 July 2012
Date of last renewal: 05 July 2017

10 DATE OF REVISION OF THE TEXT

January 2019