1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Ceftiofur 50 mg
(as Ceftiofur hydrochloride)

Excipients:

Qualitative composition of excipients and other constituents
Hydrogenated soya lecithin
Sorbitan oleate
Cottonseed oil
Water for injections

White to off white coloured suspension.

3. CLINICAL INFORMATION

3.1 Target species

Pigs.
Cattle.

3.2 Indications for use for each target species

Infections associated with bacteria sensitive to ceftiofur:

In pigs:
-Treatment of bacterial respiratory disease associated with *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Streptococcus suis*.

In cattle:
-Treatment of bacterial respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni (*previously *Haemophilus somnus)*.

-Treatment of acute interdigital necrobacillosis (panaritium, foul in the foot), associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*).

-Treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with *Escherichia coli*, *Arcanobacterium 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 inject intravenously.

Do not use in cases of hypersensitivity to the active substance, to other β-lactam antibiotics or to any of the excipients.
Do not use this veterinary medicinal product in pigs with a bodyweight more than 125 kg.
Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

3.4 Special warnings

Do not use in case of known resistance to the active substance.
Cross resistance to other lactam antibiotics can be present. Do not use in cases such cross-resistance is known.

3.5 Special precautions for use

Special precautions for safe use in the target species:
In case of the occurrence of allergic reaction the treatment should be withdrawn.

This veterinary medicinal product selects for resistant strains such as bacteria carrying extended-spectrum beta-lactamases (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.
Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.
Increased use, including use of the veterinary medicinal product deviating from the instructions given in the SPC, may increase the prevalence of resistance.

Whenever possible, this veterinary medicinal product should only be used based on susceptibility testing.

This veterinary medicinal product should only be used in 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 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 veterinary medicinal product with great care to avoid exposure, taking all recommended precautions.
If you develop symptoms following exposure such as a skin rash, you should seek medical advice 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.
Wash hands after use.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Pigs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports)	Hypersensitivity reaction[1]; Allergic reaction (e.g. allergic skin reaction[2], anaphylaxis[2]). Injection site reaction[3] (e.g. injection site skin discoloration[4]).

[1] Unrelated to dose.
[2] Treatment should be stopped immediately.
[3] Mild.
[4] Of the fascia or fat and observed up to 20 days after injection.

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports)	Hypersensitivity reaction[1]; Allergic reaction (e.g. allergic skin reaction[2], anaphylaxis[2]). Injection site inflammation[3] (e.g. injection site oedema, injection site discoloration[4]).

[1] Unrelated to dose.
[2] Treatment should be stopped immediately.
[3] Mild.
[4] Of the subcutaneous tissue and/or fascial surface of the muscle which may persist for 28 days or more after injection.

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

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Pregnancy and lactation:
Laboratory studies have not produced any evidence of a teratogenic, foetotoxic or maternotoxic effects. 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 cephalosporins are antagonized by simultaneous use of bacteriostatic antibiotics (macrolides, sulfonamides and tetracyclines).

3.9 Administration routes and dosage

Pigs: intramuscular use.
Cattle: subcutaneous use.

Pigs:
Bacterial respiratory disease:
3 mg ceftiofur/kg bw/day for 3 days (corresponding to 1 ml of the veterinary medicinal product /16 kg bw/day).

The maximum injection volume must not exceed 4 ml per injection site.
Each injection must be given at separate sites, with no overlap of subsequent injections.

Cattle:
Bacterial respiratory disease:

1 mg ceftiofur/kg bw/day for 3 to 5 days (corresponding to 1 ml of the veterinary medicinal product /50 kg bw/day).

Acute interdigital necrobacillosis:
1 mg ceftiofur/kg bw/day for 3 days (corresponding to 1 ml of the veterinary medicinal product /50 kg bw/day).

Acute post-partum metritis within 10 days after calving:
1 mg ceftiofur/kg bw/day for 5 consecutive days (corresponding to 1 ml of the veterinary medicinal product /50 kg bw/day).
In case of acute post-partum metritis, additional supportive therapy might be required in some cases.

Each injection must be given at separate sites, with no overlap of subsequent injections.

To ensure a correct dosage body weight should be determined as accurately as possible.
Before use shake the bottle for 15 seconds or until the veterinary medicinal product appears adequately resuspended.
As the vial cannot be broached more than 40 times, the user should choose 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 administered intramuscularly 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: 8 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 cephalosporin, which is active against many Gram-positive and Gram-negative bacteria. Ceftiofur inhibits the bacterial cell wall synthesis, thereby exerting 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 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* (previously *Haemophilus somnus*); bacteria involved in acute bovine foul in the foot (interdigital necrobacillosis) in cattle: *Fusobacterium necrophorum, Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli, 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, year)	MIC range (µg/mL)	MIC_{90} (µg/mL)
Actinobacillus pleuropneumoniae (220, 2014)	0.004 – 0.06	0.03
Pasteurella multocida (230, 2014)	≤ 0.002 - 0.015	0.015
Streptococcus suis (182, 2014)	0.03 - 2	0.25

Cattle

Organism (number of isolates, year)	MIC range (µg/mL)	MIC_{90}(µg/mL)
Mannheimia haemolytica (138, 2014)	≤ 0.002 - 0.03	0.0015
Pasteurella multocida (231, 2014)	≤ 0.002 - 0.06	0.008
Histophilus somni (24)	≤ 0.03 *	≤ 0.03
Arcanobacterium pyogenes (123)	≤ 0.03 - 0.5	0.25
Escherichia coli (2731)	0.125 - 2	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	(S) Susceptible
18 - 20	3-7	(I) Intermediate
≤ 17	≥ 8	(R) Resistant

No breakpoints have been determined to date for the pathogens associated with foul in the foot 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 7.34 µg/mL were reached after 1.33 hours; the terminal elimination half-life (t½) of desfuroylceftiofur was 10.9 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 occurs mainly via the urine and partly in the faeces. Ceftiofur is completely bioavailable following intramuscular administration.

After a single 1 mg/kg dose given subcutaneously to cattle, maximum plasma levels of 2.87 µg/mL are reached at 4 hours after administration. The terminal elimination half-life (t½) of desfuroylceftiofur in cattle is 10.0 hours. No accumulation was observed after a daily treatment over 5 days. Elimination occurs mainly via the urine and partly 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.
Protect from frost.

5.4 Nature and composition of immediate packaging

Type II glass vial, of 50 ml, 100 ml and 250 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.

Pack sizes:

Cardboard box containing 1 vial of 50 ml, 100 ml or 250 ml.
Polysterene box containing 15 vials of 50 ml.
Polysterene box containing 12 vials of 100 ml.
Polysterene box containing 6 vials of 250 ml.

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

Alfasan Nederland B.V.

7. MARKETING AUTHORISATION NUMBER(S)

VPA10980/013/001

8. DATE OF FIRST AUTHORISATION

02/03/2012

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

30/07/2026

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).