Summary of Product Characteristics

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 substance: Ceftiofur 50.0 mg (as Ceftiofur hydrochloride)

Excipients:
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suspension for injection. White to off white coloured suspension.

4 CLINICAL PARTICULARS

4.1 Target Species

Pigs (''weighing up to 125 kg''). Cattle.

4.2 Indications for use, specifying the 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*.
This product is not to be used in pigs with a bodyweight more than 125 kg.

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.

4.3 Contraindications

Do not inject intravenously.
Do not administer to an animal previously found to be hypersensitive to ceftiofur and other ß-lactam antibiotics or to any of the excipients.
Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

4.4 Special warnings for each target species

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.

4.5 Special precautions for use

Shake the bottle well before use to bring the product back into suspension.

Special precautions for use in animals

In case of the occurrence of allergic reaction the treatment should be withdrawn.

This 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 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, this 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 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. Handle this 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 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)

Hypersensitivity reactions unrelated to dose can occur. Allergic reactions (e.g. skin reactions, anaphylaxia) may occasionally occur. In case of the occurrence of allergic reaction the treatment should be withdrawn.

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 inflammatory reactions at the injection site, such as 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.

4.7 Use during pregnancy, lactation or lay

Laboratory studies have not produced any evidence of a teratogenic, foetotoxic or maternotoxic effects. The safety of the veterinary medicinal product has not been established in the target species during pregnancy and lactation. Use only accordingly 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 cephalosporins are antagonised by simultaneous use of bacteriostatic antibiotics (macrolides, sulfonamides and tetracyclines).

4.9 Amounts to be administered and administration route

Pigs:

Bacterial respiratory disease: 3 mg ceftiofur /kg bw/day for 3 days via intramuscular route, i.e. 1 ml/16 kg bw at each injection. 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. This product is not to be used in pigs with a bodyweight more than 125 kg.

Cattle:
Bacterial 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.
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 to avoid underdosing.
Before use shake the bottle for 15 seconds or until the product appears adequately resuspended.
As the vial cannot be broached more than 40 times, the user should choose the most appropriate vial size.

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

5 PHARMACOLOGICAL or IMMUNOLOGICAL 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.

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 *Haemophilussomnus*); 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 (microgram/mL)	MIC_{90} (microgram/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 (microgram/mL)	MIC_{90}(microgram/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 (microgram/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.

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 7.34 microgram/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 microgram/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogenated soya lecithin
Sorbitan oleate
Cottonseed oil
Water for injections

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: 3 years
Shelf-life after first broaching of the container: 28 days.

6.4 Special precautions for storage

Do not refrigerate or freeze. Protect from frost.

6.5 Nature and composition of immediate packaging

Carton box containing one glass vial, type II 50 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.
Polystyrene box containing 15 glass vials, type II 50 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.
Carton box containing one glass vial, type II 100 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.
Polystyrene box containing 12 glass vials, type II 100 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.
Carton box containing one glass vial, type II 250 ml, sealed with a bromobutyl rubber stopper and aluminium overseal.
Polystyrene box containing 6 glass vials, type II 250 ml, sealed with bromobutyl rubber stopper and aluminium overseal.

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 product should be disposed of in accordance with nation local requirements.

7 MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V
Kuipersweg 9
3449 JA Woerden
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

VPA10980/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2012
Date of last renewal: 24 March 2016

10 DATE OF REVISION OF THE TEXT

February 2017