PROPOSED PACKAGE INSERT (Clean)

VETERINARY MEDICINE

PROPRIETARY NAME

CEVAXEL RTU®

SCHEDULING STATUS

S4

DOSAGE FORM

Sterile Suspension for Injection

COMPOSITION

Ceftiofur (as hydrochloride) 50 mg per mℓ

Excipients:

Anhydrous colloidal silica

Sorbitan oleate

Propylene glycol dicaprylcaprate

PHARMACOLOGICAL CLASSIFICATION

C 17.1.1.2 Cephalosporins

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

CEVAXEL RTU contains the hydrochloride salt of ceftiofur. Ceftiofur is a third-generation broad spectrum cephalosporin, which is active against many Gram-positive and Gram-negative bacteria, including ß–lactamase producing strains.

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

NS

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. by altering or acquiring penicillin binding proteins insensitive to an otherwise effective ß-lactam;
2. by altering the permeability of the cell to ß-lactams;
3. by producing ß-lactamases that cleave the ß-lactam ring of the molecule, or
4. by 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, ß-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 in cattle against:

- bacteria involved in respiratory disease: *Pasteurella multocida*, *Mannheimia* spp., *Histophilus somni*;
- bacteria involved in acute interdigital necrobacillosis (foot rot): *Fusobacterium necrophorum*, *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*); and
- bacteria associated with acute post-partum (puerperal) metritis: *Escherichia coli*, *Arcanobacterium pyogenes* and *Fusobacterium necrophorum*.

The following Minimum Inhibitory Concentrations (MIC) have been determined for ceftiofur in European isolates (France, United Kingdom, Netherlands, Denmark, Germany, Belgium, Italy, Czech Republic, Ireland, Poland and Spain) collected from diseased animals between 2000 to 2012:

NS

Bacteria species	Origin	Year	Nb of strains	MIC of ceftiofur (µg/mL)		
				Range	MIC_{50}	MIC_{90}
Pasteurella multocida	Cattle	2009 to 2012	149	≤0.002 – 0.12	0.015	0.015
	Pigs	2009 to 2012	152	≤0.002 – 0.06	0.04	0.04
Mannheimia haemolytica	Cattle	2009 to 2012	149	≤0.002 – 0.12	0.015	0.015
Histophilus somni	Cattle	2009 to 2012	66	≤0.002-0.008	≤0.002	0.004
Escherichia coli	Cattle	2005 – 2006	163	0.06 – 1	0.23	0.44
Arcanobacterium pyogenes	Cattle	2007 – 2008	30	0.06 – 0.25	0.09	0.12
Fusobacterium necrophorum	Cattle	2000 to 2006	27	0.015 – 16	0.1	0.2
Actinobacillus pleuropneumoniae	Pigs	2009 to 2012	157	0.008-2	0.015	0.03
Streptococcus suis	Pigs	2009 to 2012	151	–0.06-16	0.12	0.5

The following ceftiofur breakpoints are used: ≤2 microgram/mL (Susceptible), 4 microgram/mL (Intermediate) and ≥8 microgram/mL (Resistant). No breakpoints have been determined to date for the pathogens associated with foot rot or acute post-partum metritis in cows.

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 13.2 microgram/mL were reached after 2 hours; the terminal elimination half-life (t½) of desfuroylceftiofur was 16.4 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 2.82 microgram/mL are reached within 4 hours after administration. In other studies, on healthy cows, a Cmax of 2.25 microgram/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 microgram/mL and 0.98 microgram/mL, respectively.

The terminal elimination half-life (t½) of desfuroylceftiofur in cattle is 12.1 hours. No accumulation was observed after a daily treatment over 5 days. The elimination occurs mainly via the urine (more than 55 %) and the faeces (30 %). Ceftiofur is completely bioavailable following subcutaneous administration.

INDICATIONS

CEVAXEL RTU® is a third generation of cephalosporin, which is active against many Gram-positive and Gram-negative bacteria, it is indicated for infections associated with bacteria sensitive to ceftiofur.

In Cattle

For the treatment of bacterial respiratory disease associated with *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somi*.

For the treatment of acute interdigital necrobacillosis (panaritium, foot rot), associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*).

For 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*: this indication is restricted to cases where treatment with another antimicrobial has failed.

In Swine (Pigs)

NS

For the treatment of bacterial respiratory disease associated with *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Streptococcus suis*.

CONTRA-INDICATIONS

Do not administer to an animal previously found to be hypersensitive to ceftiofur and other ß-lactam antibiotics.

Do not inject intravenously.

Do not use where resistance to other cephalosporins or beta-lactam antibiotics has occurred.

Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

WARNINGS OR WITHDRAWAL PERIOD IN THE CASE OF FOOD PRODUCING ANIMALS

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

Withdrawal Periods

Cattle:

Meat and offal: 8 days.

Milk: zero hours.

Pigs:

Meat and offal: 5 days.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

Hypersensitivity reactions (e.g. skin reactions, anaphylaxis) have been reported in very rare cases. In case of the occurrence of hypersensitivity reaction the treatment should be withdrawn.

NS

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, thickening of connective tissue and discoloration of the subcutaneous tissue and/or fascial surface of the muscle may be observed in rare cases. Clinical resolution is reached in most animals by 10 days after injection although slight tissue discoloration may persist for 28 days or more.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

Use during pregnancy or lactation

Studies in laboratory animals have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. The safety of the product has not been established in sows or cows during pregnancy and lactation. Use only according to a benefit/risk assessment by the responsible veterinarian.

Special precautions for use in animals

Do not use as prophylaxis in case of retained placenta.

This 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 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

NS

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 heard health programmes. Treatment of groups of animals should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

Special precautions to be taken by the person administering the 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. 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.

Interaction with other medical products

NS

The bactericidal properties of cephalosporins are antagonized by simultaneous use of bacteriostatic antibiotics (macrolides, sulfonamides and tetracyclines).

KNOWN SIGNS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

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.

QUANTITY AND STRENGTH OF ACTIVE INGREDIENTS PER DOSAGE UNIT

Ceftiofur (as hydrochloride) 50 mg per mℓ

DOSAGE AND DIRECTIONS FOR USE

For Cattle

For subcutaneous use

- Respiratory disease: 1 mg ceftiofur (as hydrochloride)/kg /day for 3 to 5 days, i.e. 1 ml/50 kg at each injection.
- Acute interdigital necrobacillosis: 1 mg ceftiofur (as hydrochloride)/kg /day for 3 days, i.e. 1 ml/50 kg at each injection.
- Acute post-partum metritis within 10 days after calving: 1 mg ceftiofur (as hydrochloride)/kg /day for 5 consecutive days, i.e. 1 ml/50 kg at each injection.

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

For Swine

For intramuscular use

3 mg ceftiofur (as hydrochloride)/kg /day for 3 days, i.e. 1 ml/16 kg at each injection.

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

To ensure a correct dosage, body weight should be determined as accurately as possible in order to avoid under-dosing.

Subsequent injections must be given at different sites.

As the vial cannot be broached more than 50 times, the user should choose the more appropriate vial size.

IDENTIFICATION

Pre-shaking - Oily beige suspension for injection

After-shaking - Oily beige suspension for injection

PRESENTATION

Multi-layer Translucent PP/Ethylene vinyl alcohol/PP multi-layer plastic vials closed with Type 1 Chlorobutyl rubber stopper crimped with aluminium cap and plastic flip capsule as follows:

Cardboard carton containing one 100 ml vial

Cardboard carton containing one 250 ml vial

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Keep out of reach of children and uninformed persons.

Store at or below 25˚C.

Keep the vial in the carton in order to protect from light.

Shelf-life after first broaching the vial is 28 days.

The vial may be punctured up to 50 times at most and should be disposed.

Any unused portion must be discarded according to pharmaceutical waste management.

REGISTRATION NUMBER

To be allocated

NS

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ceva Animal Health (Pty) Ltd.

Co. Reg. No. 1973/016009/07

PO Box 7707

HALFWAY HOUSE

1685

Tel: (+27) 11 312 4088

DATE OF NOTIFICATION OF APPROVAL OF THE SCIENTIFIC IN PACKAGE INSERT

12 October 2021

NS