SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EFICUR 50 mg/ml suspension for injection for pigs and cattle.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:
Active substance:

Ceftiofur ..... 50 mg (as Ceftiofur Hydrochloride)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
A white or yellowish 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:

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

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 (Porphyromonas asaccharolytica).*

- For the 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* (restricted to cases where treatment with another antimicrobial has failed).

4.3 Contraindications

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

None.

4.5 Special precautions for use

Special precautions for use in animals
Shake the bottle well before use to bring the product back into suspension.
In case of the occurrence of allergic reaction the treatment should be withdrawn.
Ceftiofur 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, ceftiofur 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, ceftiofur should only be based on susceptibility testing.
Ceftiofur 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 (see section 4.2 Indications for use, specifying the target species).
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.
People with known hypersensitivity to penicillins or cephalosporins should avoid contact with the product.
In the case of accidental self-injection or following exposure, if you develop symptoms such as a skin rash, seek medical advice immediately 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.

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 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

Studies in laboratory species have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. The safety of the veterinary medicinal product has not been established 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 interaction

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 by intramuscular injection, i.e. 1 ml of the product /16 kg bw/day.

Cattle:
Treatment of respiratory disease: 1 mg ceftiofur/kg bw/day for 3 to 5 days by subcutaneous injection, i.e. 1 ml of the product /50 kg bw/day.
Treatment of acute interdigital necrobacillosis: 1 mg ceftiofur/kg bw/day for 3 days by subcutaneous injection, i.e. 1 ml of the product/50 kg bw/day.

Acute post-partum metritis within 10 days after calving: 1 mg ceftiofur/kg bw/day for 5 consecutive days by subcutaneous injection, i.e. 1 ml of the product /50 kg bw/day.
Subsequent injections must be given at different sites.
In case of acute post-partum metritis, additional supportive therapy might be required in some cases.
To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

Shake well before use.

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: 5 days.

Cattle:
- Meat and offal: 8 days
- Milk: zero days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials, third generation cephalosporins.
ATCvet code: QJ01DD90.

5.1 Pharmacodynamic properties

Ceftiofur is a third generation cephalosporin, which is active against Gram-positive and Gram-negative bacteria. Like all beta-lactam antibiotics, ceftiofur inhibits bacterial cell wall synthesis, thereby exerting bactericidal properties.

Cell wall synthesis is dependent on enzymes that are called penicillin-binding proteins (PBPs). Bacteria may develop resistance to cephalosporins by 1) having penicillin binding proteins insensitive to an otherwise effective β-lactam; 2) altering cell membrane permeability to β-lactams; 3) producing β-lactamases that cleave the β-lactam ring of the antibiotic, or 4) active efflux.

Some β-lactamases, documented in Gram-negative enteric organisms, may lead to varying degrees of cross resistance between cephalosporins, as well as with penicillins, ampicillins and β-lactam inhibitor combinations.

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): *Fusobacterium necrophorum*, *Bacteroides melaninogenicus (Porphyromonas asaccharolyitica);* 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::

PIGS		
Organism (number of isolates)	**MIC range (µg/mL)**	**MIC_{90} (µg/mL)**
A. pleuropneumoniae (28)	≤ 0.03*	≤ 0.03
Pasteurella multocida (37)	≤ 0.03-0.13	≤ 0.03
Streptococcus suis (495)	≤ 0.03-0.25	≤ 0.03

CATTLE		
Organism (number of isolates)	**MIC range (µg/mL)**	**MIC_{90} (µg/mL)**
Mannheimia spp. (87)	≤ 0.03*	≤ 0.03
P. multocida (42)	≤ 0.03-0.12	≤ 0.03
H. somni (24)	≤ 0.03*	≤ 0.03
Arcanobacterium pyogenens (123)	≤ 0.03-0.5	0.25
Escherichia coli (188)	0.13 - > 32.0	0.5
Fusobacterium necrophorum (67) (from cases of foot rot)	≤ 0.06-0.13	ND
Fusobacterium necrophorum (2) (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 NCCLS 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. It is reversibly bound to plasma proteins and as a result, the metabolite concentrates at sites of infection. It remains active in the presence of necrotic tissue and debris.

Pigs
A single intramuscular dose of the product at 3 mg ceftiofur/kg body weight resulted in mean Cmax of approximately 9 microgram/mL after about 1 hour. The terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur was about 23 hours. No accumulation of desfuroylceftiofur has been observed after a dose of 3 mg ceftiofur/kg bw/day administered daily over 3 days.

Elimination occurs mainly via the urine (more than 70%); 12-15 % is eliminated via faeces.
Ceftiofur is completely bioavailable following intramuscular administration.

Cattle
A single subcutaneous dose of the product at 1 mg ceftiofur/kg resulted in mean Cmax of approximately 2 microgram/mL after about 2.5 hours. After administration of the product, the terminal elimination half-life (t1/2) of desfuroylceftiofur in cattle is approximately 18 hours.

In other studies in healthy cows, a mean C_{max} of approximately 2.25 microgram/mL was reached in the endometrium about 5 hours after a single administration of cefiofur. Maximum mean concentrations reached in caruncles and lochiae of healthy cows were about 1 microgram/mL.
No accumulation of desfuroylceftiofur has been observed after a daily treatment of ceftiofur over 5 days. Elimination occurs mainly via the urine (more than 55%). 31% is eliminated in the faeces.
Ceftiofur is completely bioavailable following subcutaneous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium monostearate
Sorbitan oleate
Triglycerides, medium-chain.

6.2 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

Glass and PET bottles
Do not store above 25 ºC.
Do not refrigerate or freeze.

PET bottles
Keep the PET bottles in the outer carton in order to protect from light

6.5 Nature and composition of immediate packaging

Type II glass bottles of 50, 100 and 250 ml.
Polyethylene terephthalate (PET) bottles of 50, 100 and 250 ml.
The bottles are closed with a Type I bromobutyl closure and aluminium cap
The 250 ml glass bottle has a colourless plastic package as a protective measure in order to avoid glass bottle breaking when it is being used.

Pack sizes:
Cardboard box with 1 glass bottle of 50 ml.
Cardboard box with 1 glass bottle of 100 ml.
Cardboard box with 1 glass bottle of 250 ml.
Cardboard box with 10 glass bottles of 100 ml.
Cardboard box with 12 glass bottles of 100 ml.

Cardboard box with 1 PET bottle of 50 ml.
Cardboard box with 1 PET bottle of 100 ml.
Cardboard box with 1 PET bottle 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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios Hipra SA
Avda La Selva 135
17170 Amer (Girona)
Spain

8. MARKETING AUTHORISATION NUMBER

Vm 17533/4010

9. DATE OF FIRST AUTHORISATION

07 January 2009

10 DATE OF REVISION OF THE TEXT

May 2015

APPROVED T. NASH **30/07/15**