1.B.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ceftionil 50 mg/ml suspension for injection for pigs and cattle [CZ, IT, SK]
Cefaven 50 mg/ml suspension for injection for pigs and cattle [HU, PL]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substance:
Ceftiofur (as ceftiofur hydrochloride)…… 50.0 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection.
A white or slightly yellow coloured opaque 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 *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*, *Trueperella pyogenes (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 use in case of hypersensitivity to the active substance, to other beta-lactam antibiotics or to any of the excipients

Do not inject intravenously.
Do not use in poultry (including eggs) due to risk of spread antimicrobial resistance to humans.
Do not use in cases where resistance to ceftiofur or to other cephalosporins or beta-lactam antibiotics has occurred.

4.4 Special warnings for each target species

None

4.5 Special precautions for use

Special precautions for use in animals
CEFTIONIL/CEFAVEN 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, CEFTIONIL/CEFAVEN 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, CEFTIONIL/CEFAVEN should only be used based on susceptibility testing.
CEFTIONIL/CEFAVEN 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 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.

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.

Handle this product with great care to avoid exposure. Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician

4.6 Adverse reactions (frequency and seriousness)

In case of the occurrence of allergic reaction the treatment should be withdrawn.

In very rare cases the following adverse reactions may occur:
- Hypersensitivity reactions unrelated to dose.
- Allergic reactions (e.g. skin reactions, anaphylaxia). In case of the occurrence of allergic reaction the treatment should be withdrawn.

-In pigs, mild reactions at the injection site, such residual lesions in the intermuscular connective tissue consisting of round clear areas, have been observed in some animals for up to 20-22 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 32 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).

4.7 Use during pregnancy, lactation or lay

Studies in laboratory species have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. Safety has not been established in the target species during pregnancy or lactation. Use only accordingly 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 cephalosporins are antagonized by simultaneous use of bacteriostatic antibiotics (macrolides, sulphonamides and tetracyclines).

4.9 Amounts to be administered and administration route

Pigs: intramuscular use
3 mg ceftiofur/kg bw/day, corresponding to 1 ml/16 kg bw/day for 3 days

Cattle: subcutaneous use
-Respiratory disease: 1 mg ceftiofur /kg bw/day, corresponding to 1 ml/50 kg bw/day for 3 to 5 days.
-Acute interdigital necrobacillosis: 1 mg/kg bw/day, corresponding to 1 ml/50 kg bw/day for 3 consecutive 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, corresponding to 1 ml/50 kg bw/day for 5 consecutive days
In case of acute post-partum metritis, additional supportive therapy might be required in some cases
A maximum volume of 6 ml may be administered in each injection site.

Subsequent injections must be given at different sites.
To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.
As the vial cannot be broached more than 40 times, the user should choose the more appropriate vial size.
Shake the bottle well for 30 seconds before use to bring the veterinary medicinal product back into suspension.

4.10 Overdose (symptoms, emergency procedures, 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 intramuscularly administered for 15 consecutive days.
In cattle, no signs of systemic toxicity have been observed following substantial parenteral overdosages.

4.11 Withdrawal period

Pigs:
- Meat and offal: 5 days.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation Cephalosporins.
ATC Vet Code: QJ01DD90.

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.
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) 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*; bacteria involved in acute bovine foot rot (interdigital necrobacillosis) in cattle: *Fusobacterium necrophorum*, *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli*, **Trueperella pyogenes (***Arcanobacterium pyogenes)* and *Fusobacterium necrophorum.*

Minimal inhibitory concentration breakpoints (µg/ml) for sensitivity (S), intermediate sensitivity (I) and resistance (R) of ceftiofur against bovine and porcine respiratory pathogens (CLSI, 2013):

	S	I	R
Bovine respiratory disease Mannheimia haemolytica Pasteurella multocida Histophilus somni **Porcine respiratory disease** Actinobacillus pleuropneumoniae Pasteurella multocida Streptococcus suis	≤ 2	4	≥ 8

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 9.6 µg/mL ± 2.9 were reached after 2 hour; the terminal elimination half-life (t½) of desfuroylceftiofur was 16.6 ± 3.2 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 2.4 ± 0.7 µg/mL are reached within 2.8 hours after administration. In healthy cows, a C_{max} 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 9.0 ± 1.9 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

Hydrogenated soya lecithin
Sorbitan oleate
Cottonseed oil

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
This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging
Cardboard boxes with one 100 ml or one 250 ml plastic bottle of polypropylene with closures of bromobutyl rubber and aluminium cap.
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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios e Industrias IVEN, S.A.
Luís I, 56
28031 MADRID (Spain)

8. MARKETING AUTHORISATION NUMBER
…….

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD/MM/YYYY
Date of last renewal: DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

MM/YYYY

PROHIBITION OF SALE, SUPPLY AND/OR USE

For animal treatment only – to be supplied only on veterinary prescription.