CONSUMER PACKAGE INSERT FOR A VETERINARY PREPARATION

The medicine is dispensed with a veterinarian's prescription only

For animal use only

1. NAME, FORM AND STRENGTH OF THE VETERINARY MEDICINE

Excenel RTU Fluid Veterinary suspension for intramuscular and subcutaneous injection

2. ACTIVE INGREDIENT

Ceftiofur (as hydrochloride) 50 mg/ml

The list of inactive ingredients is in section 13.

3. WHAT IS THE MEDICINE INTENDED FOR?

For treatment of 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* (former *Pasteurella haemolytica*), *Pasteurella multocida* and *Histophilus somni* (former *Haemophilus somnus*).

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: *Arcanobacterium pyogenes, Escherichia coli* and *Fusobacteriu necrophorum* sensitive to ceftiofur where treatment with another antimicrobial agent has failed.

Therapeutic group:

Antibacterials for systemic use. Third-generation cephalosporins.

4. CONTRAINDICATIONS

Do not use if the animal has a known hypersensitivity to ceftiofur and other beta-lactam antibiotics.

Do not inject intravenously.

Do not use in case of resistance to cephalosporins or to other beta-lactam antibiotics.

Do not use in poultry (including egg laying poultry), to prevent spread of variants resistant to the preparation to humans.

5. SIDE EFFECTS

Hypersensitivity reactions unrelated to the dosage can occur. Allergic reactions (e.g., skin reactions or anaphylaxis) have very rarely been reported (fewer than one in 10,000 animals, including isolated incidents).

In swine, mild reactions at the injection site, such as: discoloration of the fascia or fat, have been observed in very rare cases up to 20 days after injection.

In cattle, reactions at the injection site, such as stiffness and swelling after subcutaneous injection, have been observed. Mild to moderate chronic inflammation at the injection site has been observed in most animals up to 42 days after injection. Injection site reactions have been reported very rarely in field studies.

Side effects can be reported to the Ministry of Health via an online form for reporting side effects found on the Ministry of Health homepage www.health.gov.il, or via the following link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

6. TARGET SPECIES

Cattle, pigs

7. METHOD OF ADMINISTRATION AND DOSAGE

Suspension for intramuscular and subcutaneous injection.

Pigs

3 mg ceftiofur/kg body weight/day for 3 days by intramuscular injection, i.e., 1 ml for 16 kg body weight in each injection.

Do not inject more than 4 ml into a single injection site.

Cattle

Respiratory diseases: 1 mg ceftiofur/kg body weight/day for 3 to 5 days by subcutaneous injection, i.e., 1 ml for 50 kg body weight at each injection.

Acute foot rot: 1 mg ceftiofur/kg body weight/day for 3 days by subcutaneous injection, i.e., 1 ml for 50 kg body weight at each injection.

For treatment of acute post-partum metritis within 10 days after calving: 1 mg ceftiofur/kg body weight/day for 5 consecutive days by subcutaneous injection, i.e., 1 ml for 50 kg body weight at each injection.

Do not inject more than 13 ml into a single injection site.

Subsequent injections must be given at different sites.

100 ml vials can be punctured up to 50 times. Otherwise, a multi-dose syringe is recommended.

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

8. HOW TO USE THE PREPARATION

Before use, shake the bottle vigorously for 60 seconds or until the product appears adequately resuspended.

To ensure a correct dosage, the animal's body weight should be determined as accurately as possible to avoid underdosing.

9. WITHDRAWAL PERIOD

Pigs: 2 days

Cattle: 6 days for meat
0 hours for milk

10. WARNINGS

- Special warnings relating to safety of use of the medicine in animals

Shake the bottle well before use to resuspend the suspension.

If an allergic reaction occurs, stop the treatment.

Excenel RTU Fluid Veterinary is intended for resistant bacterial strains such as bacteria containing extended spectrum beta-lactamases (ESBL). Spread of these strains (e.g., via food) may constitute a risk to human health; therefore, this preparation should be used after failure to obtain an adequate clinical response, or when an adequate clinical response is not expected (in acute cases where immediate treatment is necessary without a bacteriological diagnosis) to first-line narrow-spectrum antibiotics. Excessive use, including a use not indicated in the leaflet, may increase the prevalence of strains resistant to Excenel RTU Fluid Veterinary. If possible, use this preparation only following a sensitivity test.

Do not use as prophylaxis in case of retained placenta.

The preparation is intended for use in individual animals. Do not use as prophylaxis or as part of a herd health program. Use in groups of animals must be limited to prolonged disease outbreaks, as per approved conditions of use.

- Special warnings relating to the safety of the person administering the preparation

Injection, inhalation, ingestion or skin contact of penicillins and cephalosporins may cause hypersensitivity (allergic reaction). Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may be serious.

If you have a known sensitivity, or if you have been told not to work with these preparations, do not come into contact with the preparation.

If you develop symptoms such as skin rash after exposure to the preparation, refer for medical assistance and show these warnings to the doctor.

More serious symptoms including: swelling of the face, lips or eyes or difficulty with breathing, require urgent medical attention.

Wash hands after use.

- Pregnancy and lactation

Although studies in laboratory animals have not shown a teratogenic effect, miscarriage or effect on fertility, the safety of this preparation with regard to fertility has not been tested in pregnant cows or pigs.

The veterinarian must only use the preparation according to the benefit versus risk assessment.

- Interactions with other medicines and other forms of interactions

The bactericidal properties of beta-lactams are neutralized when used concomitantly with bacteriostatic antibiotics (e.g., macrolides, sulfonamides and tetracyclines).

Aminoglycosides may increase the effect of cephalosporins.

- Overdose

The low toxicity of ceftiofur has been demonstrated in pigs upon administration of ceftiofur sodium at a dosage 8 times higher than the recommended daily dose for intramuscular administration for 15 consecutive days. In cattle, no systemic toxicity has been observed following parenteral overdose.

- Incompatibility

Due to the absence of compatibility studies, do not mix the preparation with other veterinary preparations.

11. STORAGE INSTRUCTIONS

Do not use the medicine after the expiry date (**exp. Date**) appearing on the package. The expiry date refers to the last day of that month.

Shelf-life after first opening: 30 days.

Keep out of reach of children.

Store below 25°C.

12. INSTRUCTIONS REGARDING DISPOSAL THE PREPARATION/ REMNANTS OF THE PREPARATION AFTER USE

All veterinary medicinal preparations that were not used, or any leftover substances obtained upon use of a veterinary medicinal product, must be discarded as toxic waste; do not discard via wastewater.

13. FURTHER INFORMATION

- **Pharmacodynamics**

Ceftiofur is a new-generation cephalosporin, which is active against many Gram-positive and Gram-negative bacteria. Ceftiofur inhibits bacterial cell wall synthesis, thereby exerting bactericidal properties.

Beta-lactams (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 the following four main mechanisms: 1) altering or acquiring PBP's insensitive to an otherwise effective beta-lactam; 2) altering the permeability of the cell to beta-lactams; 3) producing beta-lactamases that cleave the beta-lactam ring of the molecule, or 4) active efflux of the preparation.

Some beta-lactamases discovered in Gram-negative enteric bacteria, may elevate MIC by varying degrees to third- and fourth-generation cephalosporins, as well as to penicillins, ampicillins, beta-lactam inhibitor combinations, and first- and second-generation cephalosporins.

Ceftiofur is active against the following bacteria which are involved in respiratory diseases in pigs: *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Streptococcus suis*.

Bordetella bronchiseptica is not sensitive to ceftiofur.

The preparation is also active against bacteria involved in respiratory diseases in cattle:

Pasteurella multocida

Mannheimia haemolytica (former Pasteurella haemolytica)

Histophilus somni (former Haemophilus somnus);

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

Arcanobacterium pyogenes

Fusobacterium necrophorum

The following minimum inhibitory concentrations (MIC) were determined for ceftiofur in target bacteria isolations performed in Europe, isolated from diseased animals:

Pigs		
Organism (number of isolates)	**MIC range (µg/ml)**	**MIC_{90} (µg/ml)**
Actinobacillus pleuropneumoniae (157)	0.008 - 2	0.03
Pasteurella multocida (152)	≤0.002 - 0.06	0.004
Streptococcus suis (151)	0.06 - ≥16	0.5
Cattle		
Organism (number of isolates)	**MIC range (µg/ml)**	**MIC_{90} (µg/ml)**
Mannheimia haemolytica (149)	≤0.002 - 0.12	0.015
Pasteurella multocida (134)	≤0.002 - 0.015	0.004
Histophilus somni (66)	≤0.002 - 0.008	0.004
Truperella pyogenes (35)	0.25 - 4	2
Escherichia coli (209)	0.13 - 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

ND: not determined.

Growth breakpoints for bovine and porcine respiratory disease bacteria, as recommended by CLSI:

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 for foot rot or acute post-partum metritis in cows.

- **Pharmacokinetics**

After administration, ceftiofur is quickly metabolized to desfuroylceftiofur, the principal active metabolite.

Desfuroylceftiofur has an anti-microbial activity identical to that of ceftiofur against the bacteria involved in respiratory diseases in animals. The active metabolite is reversibly bound to plasma proteins. Because it is transported by these proteins, it concentrates at the infection site, and remains active in the presence of the necrotic tissue and debris.

Pigs:

Upon administration of a single intramuscular dose of 3 mg/kg body weight, maximum plasma concentrations of 11.8 ± 1.67 µg/ml were reached after one hour. The terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur was 16.7 ± 2.3 hours. No accumulation of desfuroylceftiofur was observed after a dose of 3 mg ceftiofur/kg body weight/day administered for 3 days.

Clearance occurs mainly via the urine (more than 70%). Average recovery of the preparation in feces was approximately 12-15%.

Ceftiofur is completely bioavailable following intramuscular administration.

Cattle:

After a single subcutaneous 1 mg/kg dose to cattle, maximum plasma levels of 2.85 ± 1.11 µg/ml were reached within 2 hours. In healthy cows, a maximal concentration of 2.25 ± 0.79 µg/ml was reached in the endometrium within 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 of desfuroylceftiofur in cattle is 11.5 ± 2.57 hours. No accumulation was observed after a daily treatment over 5 days. Clearance occurs mainly via the urine (more than 55%); 31% of the dose was recovered in the feces.

Ceftiofur is completely bioavailable following subcutaneous administration.

- **In addition to the active ingredient, the medicine also contains**
  Polysorbate 80
  Water for injection
  Triglycerides Medium-Chain (Miglyol 812)
- **What the medicine looks like and the content of the package**
  Light-colored, opaque suspension
  100 ml
- **Package sizes**
  100 ml glass bottle
- **License Holder**
  Zoetis Israel Holding B.V., 5 Atir Yeda Street, Kfar Saba.
- **Manufacturer**
  Zoetis LLC (subsidiary of Zoetis Inc), USA
  2605 East Kilgore Road, Kalamazoo, Michigan, USA
- **This leaflet was checked and approved by the Ministry of Health in** February 2018
- **Registration number of the medicine in the National Drug Registry of the Ministry of Health:**
  084 02 92399 00

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