Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Excenel Flow, 50 mg/ml, suspension for injection for pigs and cattle

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substance:
Ceftiofur (as hydrochloride) 50.0 mg
Excipient(s): For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection. Opaque suspension, white to off-white.

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* (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 *Escherichia coli*, *Arcanobacterium pyogenes*and *Fusobacterium necrophorum*, sensitive to ceftiofur, were 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 cases 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.

4.4 Special warnings for each target species

None known.

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In case of the occurrence of allergic reaction the treatment should be withdrawn.

EXCENEL Fluid suspension (or EXCENEL Flow or Evo) selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) which may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, EXCENEL Fluid suspension (or EXCENEL Flow or Evo)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 more narrow spectrum antimicrobials 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 bacteria resistant to EXCENEL Fluid suspension (or EXCENEL Flow or Evo). Whenever possible, EXCENEL Fluid suspension (or EXCENEL Flow or Evo) should only be used based on susceptibility testing.

Do not use as prophylaxis in case of retained placenta.

EXCENEL Fluid suspension (or EXCENEL Flow or Evo)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 limited to ongoing disease outbreaks according to the approved conditions of use.

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.

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) have been reported in very rare cases (less than 1 animal in 10,000 animals, including isolated reports).

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

In cattle, firmness and swelling were observed at the injection site after SC injection of the test article. Mild to moderate local chronic inflammation was observed in most animals until 42 days post injection. Injection site reactions have been reported from the field in very rare cases.

4.7 Use during pregnancy, lactation or lay

Even though studies in laboratory animals show no evidence of teratogenesis, abortion or influence on reproduction, the reproductive safety of ceftiofur has not been specifically investigated in pregnant sows or cows.
Use only according to a benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

The bactericidal properties of Beta-lactams are neutralised by simultaneous use of bacteriostatic antibiotics (macrolides, sulfonamides and tetracyclines).
Aminoglycosides may have a potentiating effect on cephalosporins.

4.9 Amounts to be administered and administration route

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

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.

Pigs:
3 mg ceftiofur /kg bw/day for 3 days via intramuscular route, i.e. 1 ml/16 kg bw at each injection.
Not more than 4 ml should be administered per injection site.

Cattle:
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.
Not more than 13 ml should be administered per injection site.

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

Subsequent injections must be given at different sites.
50 ml and 100 ml vials can be broached a maximum of 50 times. 250 ml vials can be broached a maximum of 33 times.
Otherwise, the use of a multiple-dose syringe is recommended.

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: 2 days.
Cattle: meat and offal: 6 days; milk: zero hours.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation Cephalosporins.
ATCvet code: QJ01D D90

5.1 Pharmacodynamic properties

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

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, 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*a nd *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* (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*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)	**MIC range (microgram/mL)**	**MIC_{90} (microgram/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 (microgram/mL)**	**MIC_{90} (microgram/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.

The following breakpoints are recommended by CLSI for bovine and porcine respiratory pathogens currently on the label for EXCENEL Fluid suspension (or EXCENEL Flow or Evo) :

Zone Diameter (mm)	**MIC (microgram/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. 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 11.8 ± 1.67 microgram/mL were reached after 1 hour; the terminal elimination half-life (t½) of desfuroylceftiofur was 16.7 ± 2.3 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 2.85 ± 1.11 microgram/mL are reached within 2 hours after administration. In healthy cows, a Cmax of 2.25 ± 0.79 microgram/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 microgram/mL and 0.98 ± 0.25 microgram/mL, respectively.
The terminal elimination half-life (t½) of desfuroylceftiofur in cattle is 11.5 ± 2.57 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

Polysorbate 80
Triglycerides Medium-chain
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: 2 years.
Shelf-life after first broaching of the container: 28 days.

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and composition of immediate packaging

Cardboard box with 1 glass vial (Type I) of 50, 100 or 250 ml.
Cardboard box with 10 glass vials (Type I) of 50 or 100 ml.
50 and 100 ml vials have a chlorobutyl stopper and an aluminium overseal with plastic flip-off cap. 250 ml vial has a bromobutyl stopper and an aluminium overseal with a pull-off cap. 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 local requirements.

7 MARKETING AUTHORISATION HOLDER

Zoetis Belgium S.A.
2nd Floor, Building 10

Cherrywood Business Park, Loughlinstown
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA10387/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 1997
Date of last renewal: 07 April 2014

10 DATE OF REVISION OF THE TEXT

September 2017