1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Excede Veterinary
Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:
Active substance:
Ceftiofur (as crystalline free acid) 200mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Opaque suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, horses

4.2 Indications for use, specifying the target species

Cattle: Treatment of acute interdigital necrobacillosis in cattle also known as Panaritium or foot rot.

Treatment of acute post-partum (puerperal) metritis in cattle.

This veterinary medicinal product should only be used following antibiotic susceptibility testing, after eliminating any other possible treatment options.

Horses: Treatment of lower respiratory tract infections caused by susceptible strains of Streptococcus equi ssp. zooepidemicus.

Only after the sensitivity of the bacteria has been proven and it has been found that there is no alternative treatment (proven resistance to other agents).

4.3 Contraindications

Do not use in cases of hypersensitivity to ceftiofur or other beta-lactam antibiotics, or to any of the excipients.

4.4 Special warnings for each target species

Cattle:
Unknown

Horses:
The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea is observed, additional doses of Excede Veterinary should not

be administered, and appropriate therapy should be initiated.
Due to the extended exposure in horses, based on the drug's pharmacokinetic properties, adverse reactions may require prolonged care. Excede Veterinary is slowly eliminated from the body, with approximately 17 days needed to eliminate 97% of the dose from the body. Animals experiencing adverse reactions may need to be monitored for this duration of time.
The use of ceftiofur has not been evaluated in horses less than 4 months of age. The long term effects on injection sites have not been evaluated.

4.5 Special precautions for use

Special precautions for use in animals

For systemically administered broad spectrum cephalosporins (3rd and 4th generation, such as ceftiofur), it should be reflected that these are to be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other antimicrobials. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of bacteria resistant to ceftiofur. Official, national and regional antimicrobial policies should be taken into account when the product is used.

Whenever possible, cephalosporins should only be used based on susceptibility testing. When considering the treatment strategy, it is appropriate to consider improvement of the herd management practice and use supporting treatment with suitable local products (e.g. disinfectants).
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 such as ceftiofur may cause hypersensitivity in people and in animals 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 and cephalosporins should avoid contact with this veterinary medicinal product.
Avoid contact with skin or eyes. In the event of contact, wash with clean water for 15 minutes.
In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If you develop symptoms following exposure such as a skin rash or persistent eye irritation, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are serious reactions and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

Cattle:
Visible swellings have been noted at the injection site in about two thirds of treated animals, two days after injection in field conditions. These reactions will resolve within a maximum of 23 days. Injection site swellings may result in mild to moderate pain in some animals in the initial days following injection.

In very rare cases, sudden death has been reported following administration of the product. In such cases, death has been attributed to intra-vascular administration of the product or anaphylaxis.

Horses:
The injection of Excede Veterinary in the horse may cause firmness, swelling, sensitivity, and/or edema at the injection site.
A total of 373 horses of various breeds, ranging in age from 4 months to 20 years, were included in the field study safety analysis. Adverse reactions reported in horses treated with EXCEDE and the placebo control are summarized in Table 1. Injection site swelling (edema) was reported in 10 of 278 (3.6%) EXCEDE-treated horses and 1 of 95 (1%) of the placebo-

treated horses. Of the 10 EXCEDE-treated horses with injection site swelling, 8 horses had swellings of 4 cm or less in diameter, one horse had a 10 cm diameter swelling and one horse had injection site reactions to both injections measuring 25 x 12 cm each. The injection site reactions in EXCEDE-treated horses resolved over 1 to 20 days. At least one episode of diarrhea, loose, soft, or cowpie stools were observed in 25 of 278 (9%) of the EXCEDE-treated horses and 7 of 95 (7%) of the placebo-treated horses. The duration of episodes in EXCEDE-treated horses ranged from a single observation of loose stool to observations lasting 6 days. All cases were self-limiting and resolved with minimal (a single dose of loperamide) or no treatment.

Table 1. Number of Horses with Adverse Reactions During the Field Study with Excede Veterinary:

Adverse Reaction	Excede Veterinary (n=278)	Placebo (n=95)
Diarrhea/Soft Stool	25 (9%)	7 (7%)
Injection Site Swelling	10 (4%)	1 (1%)

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions 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).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il.

4.7 Use during pregnancy, lactation or lay

Cattle:

Pregnancy:

Laboratory studies in mice have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. Laboratory studies in rats have shown no evidence of teratogenic effects but maternotoxic (soft faeces) and foetotoxic (reduced foetal weight) effects were observed. No effects on the reproductive performance were observed in both species. No specific studies have been conducted in pregnant cows. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Lactation:

This veterinary medicinal product can be used during lactation.

Fertility:

No specific studies have been conducted in breeding cattle. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Horses:

The use of ceftiofur has not been evaluated in breeding, pregnant, or lactating horses. The long term effects on injection sites have not been evaluated.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

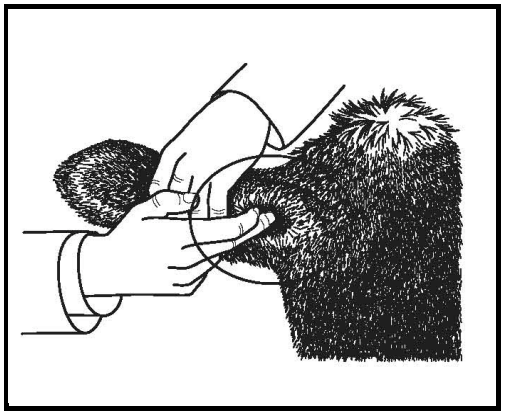
4.9 Amounts to be administered and administration route

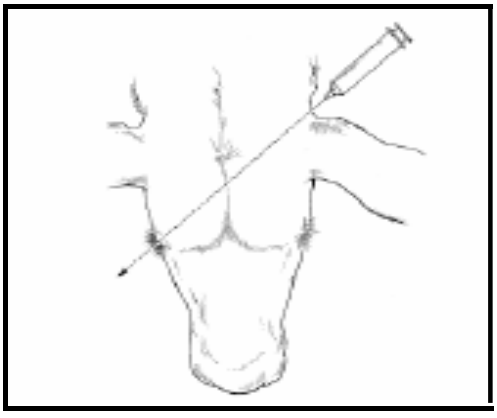
Shake the bottle vigorously for 30 seconds, or until all visual settlement has been resuspended.

Cattle:
Single subcutaneous injection of 6.6 mg ceftiofur/kg bodyweight (equivalent to 1 ml of Excede Veterinary per 30 kg bodyweight) administered at the base of the ear.
To ensure a correct dosage, bodyweight should be accurately determined to avoid under-dosing.
It is recommended to limit injection volumes to a maximum of 30 ml per injection site.

Base of the ear administration:
• Administer in the posterior part of the ear base (see Figure 1).
• Hold the syringe and insert the needle behind the animal's ear so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the animal's opposite eye (see Figure 2).
• Take appropriate precautions to avoid intra-arterial or intravenous injection, such as restraining appropriately the animal (chute or head restraint for example) and using appropriate needles [1 inch (2.54 cm) long, 16 gauge].

Figure 1. Injection location for the subcutaneous administration of Excede Veterinary at the posterior aspect of the ear where it attaches to the head (base of ear)		Figure 2. Subcutaneous administration of Excede Veterinary at the posterior aspect of the ear where it attaches to the head (base of ear). Diagram of the head showing the direction for the base of the ear injections administered toward the animal's opposite eye.





If clinical signs have not improved 48 hours after treatment, the diagnosis and treatment of the condition should be re-evaluated.

Horses:
Shake well before using.
Administer two intramuscular injections to horses, 4 days apart, at a dose of 6.6 mg/kg bodyweight

(equivalent to 1 ml of Excede Veterinary per 30 kg bodyweight). A maximum of 20 mL per injection site may be administered. Therapeutic drug concentrations are maintained for 6 days after the second injection (or a total of 10 days from the beginning of treatment) against Streptococcus equi ssp. zooepidemicus.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Cattle:
In cattle, although Excede Veterinary has not been specifically tested for overdoses, no signs of systemic toxicity related to ceftiofur have been observed following 55 mg/kg parenteral daily overdoses of ceftiofur sodium for five days.

Horses:
Two studies, a target animal safety (TAS) study and a pharmacokinetic (PK) study), were conducted to assess the safety of Excede Veterinary in the horse.
In the TAS study, healthy adult horses received 6 intramuscular (lateral neck) injections of Excede Veterinary at doses of either 1 (1X), 2 (2X) or 3 (3X) ml/kg with a 4-day interval between each injection. In the TAS study, there were no treatment related gastrointestinal findings for the three Excede Veterinary treatment groups. In the PK study, one horse treated with (2X) Excede Veterinary experienced a mild episode of colic the day after the second injection of Excede Veterinary. The horse recovered without treatment. Injection sites were observed in both studies. In both studies, the largest injection volume administered was 20 ml per injection site. There were no observations of erythema, necrosis or drainage at the injection sites in these studies. Firmness, swelling, and/or sensitivity were observed in at least one injection site in all horses treated at the label dose. In the TAS study, injection site reaction measurements ranged from no measurable reaction to 16 x 33 x 1.5 cm. In the PK study, the largest area of edema associated with the injection site ranged from no detectable reaction to a 30 x 36 cm area of edema. Injection site reactions developed within 2 days of injection and resolved within 1-18 days. In the PK study, 2 horses had small areas of firmness that had not resolved at the end of the study (21 days after injection). In both studies, a greater incidence of injection site reactions occurred after the second injection, and in several horses, swelling at the injection site resolved then recurred 1-5 days later.
In the PK study, several horses developed clinical signs consistent with foot pain (stiff in the front limbs when turned in tight circles, and increased pulses and heat to the front feet). One horse in the ceftiofur sodium group and one horse in the (2X) Excede Veterinary group were euthanized due to laminitis. Clinical signs of foot pain (stiff front limbs and increased heat and pulses in feet) affected more horses, for a longer period of time, in all Excede-treated groups as compared to the ceftiofur sodium-treated group. The study housing (multi-horse pens on concrete slabs) and diet (free choice alfalfa/grass mix and once a day pellets) may have contributed to the development of foot pain. The prevalence and severity of injection site reactions in Excede-treated horses may also have contributed to the development of a stiff gait. A causal relationship between ceftiofur and foot pain could not be definitively determined.

4.11 Withdrawal period(s)

Cattle:
Meat and offal: 9 days.
Milk: zero days.
It is essential that Excede Veterinary is only administered subcutaneously at the base of ear location in non-edible tissue, as described in section 4.9, in order to comply with the meat withdrawal period.

Horses:
Not Applicable

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, third-generation cephalosporins.
ATCvet code: QJ01DD90.

5.1 Pharmacodynamic properties

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

In cattle, ceftiofur is active against the following micro-organisms which are involved in acute post-partum (puerperal) metritis: *Escherichia coli*, *Arcanobacterium pyogenes* and *Fusobacterium necrophorum*; and interdigital necrobacillosis: *Bacteroides* spp., *Fusobacterium necrophorum*, *Porphyromonas* spp. and *Prevotella* spp.

Desfuroylceftiofur is the principal active metabolite. It has an antimicrobial activity similar to that of ceftiofur against the target pathogens.

5.2 Pharmacokinetic particulars

Cattle:
Ceftiofur is well absorbed in cattle following base of the ear injection. After administration, ceftiofur is quickly metabolised to desfuroylceftiofur, the principal active metabolite. Protein binding of ceftiofur and its major metabolite is high, approximately 70% – 90%. One hour after a single administration, plasma concentrations are greater than 1 µg/ml. Maximum concentrations in plasma (about 5 µg/ml) occurred from 12 hours following administration. Total plasma concentrations above 0.2µg/ml and 1µg/ml of ceftiofur and its active metabolites are maintained for at least 7 and 4 days, respectively.

Horses:
Ceftiofur crystalline free acid (Excede Veterinary) is rapidly metabolized to desfuroylceftiofur, the primary metabolite with antimicrobial activity.
Two intramuscular injections of Excede veterinary at a dose of 6.6 mg/kg body weight in the horse provide concentrations of ceftiofur and desfuroylceftiofur related metabolites in plasma above the therapeutic target of 0.2 µg/mL for the entire 96 hour (4 day) dosing interval and for 6 days after the second injection (or a total of 10 days from the beginning of treatment) (see Figure 3 and Table 2).

Figure 3. Average plasma concentration of ceftiofur and desfuroylceftiofur related metabolites in horses following the intramuscular administration of either Excede veterinary at a dose of 6.6 mg/kg administered twice at a 96 hour interval or ceftiofur sodium (also referred as Naxcel) at a dose of 2.2 mg/kg BW once daily for 10 consecutive days.

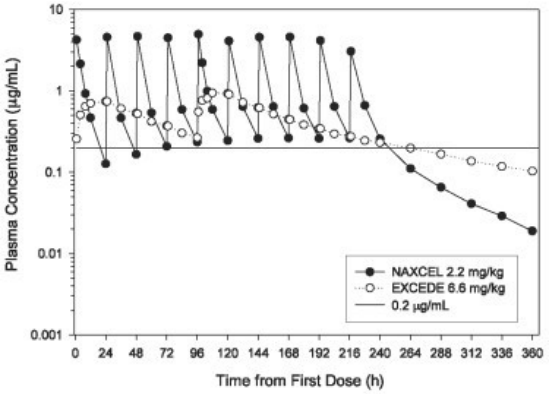


Table 2. Pharmacokinetic parameters measured after either two intramuscular injections of Excede Veterinary at a dose of 6.6 mg/kg BW at a 96 hour interval or ceftiofur sodium at a dose of 2.2 mg/kg BW once daily for 10 consecutive days are summarized in the following table.

PK Parameter	Ceftiofur crystalline free acid -SS at 6.6 mg/kg BW administered twice 96 h apart (Mean ± SD; n=12)		Ceftiofur sodium at 2.2 mg/kg BW once daily for 10 days (Mean ± SD; n=11)	
AUC 0-∞ (µg•h/mL)	157 (19.1)		353 (44.9)	
t>0.2 (h)	262 (29.0)		ND	
	Dose 1	Dose 2	Dose 1	Dose 10
Tmax (h)	21.6 (5.8)	15.6 (6.3)	1.0	2.0 (3.3)
Cmax (µg/mL)	0.78 (0.19)	1.0 (0.24)	4.31 ± 0.78	3.99 (1.23)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain
Cottonseed oil
Nitrogen

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

Do not use the veterinary medicinal product after the expiry date **(exp. date)** mentioned on the package. The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 28 days, when stored below 25 °C.

6.4 Special precautions for storage

Store at temperature below 25℃

6.5 Nature and composition of immediate packaging

Cardboard box with one type I glass vial of 100 ml with a chlorobutyl-isoprene rubber stopper and an aluminum cap.

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 from such veterinary medicinal products should be disposed of as a toxic waste. Do not dispose of in the sewage system.

7. MARKETING AUTHORISATION HOLDER

Zoetis Israel Holding B.V.,
5 Atir Yeda Street, Kfar Saba, Israel

8. MARKETING AUTHORISATION NUMBER(S)

161-89-35036-00

9. MANUFACTURER:

Zoetis LLC (subsidiary of Zoetis Inc.), 2605 East Kilgore Road, Kalamazoo, Michigan, USA

10. VETERINARY USE

The veterinary medicine is dispensed with a veterinarian's prescription only

The content of this leaflet was approved by the Ministry of Health in May 2019