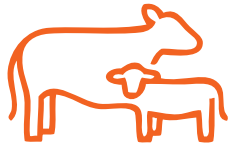


TECHNICAL BULLETIN



Efficacy and Safety of PROTIVITY™ Modified-Live *Mycoplasma bovis* Vaccine in Young Calves

Zoetis

Parsippany, NJ 07054

PROTIVITY™ is the first modified-live *Mycoplasma bovis* vaccine, offering an effective, safe, and proactive approach to the widespread problem of respiratory disease caused or exacerbated by *M. bovis*.

Summary

- PROTIVITY™ is the first and only modified-live vaccine proven to be effective against respiratory disease caused by *Mycoplasma bovis*.
- A 60-day study assessed the efficacy of PROTIVITY for protecting neonatal calves against challenge with a virulent field strain of *M. bovis*.¹ The study involved 83 healthy, young Holstein calves (male and female) 7 to 12 days of age.
 - PROTIVITY vaccination, relative to controls, generated 74% ($P < 0.0001$) reduction in the mean percentage of total lung with lesions. The mitigated fraction estimate for the median percentage of total lung with lesions was 0.66 (95% CI: 0.37, 0.90) for PROTIVITY vs controls, indicating a clinically relevant reduction in lung lesions in the vaccinated animals.
 - PROTIVITY vaccinates were protected against fever and clinical signs ($P \leq 0.05$) typically associated with *M. bovis* respiratory disease.
 - Onset of immunity was demonstrated as soon as 11 days after the second dose.
- Two field studies evaluated the safety of PROTIVITY for 8 weeks or 4 months post-vaccination in young calves reared under commercial production conditions.^{2,3}
 - No injection site reactions or abnormal events attributable to the vaccine were detected. PROTIVITY was shown to be safe for use in calves as young as 1 week of age.
- PROTIVITY offers a game-changing technological advance for veterinarians and beef producers who want to upgrade respiratory disease management.

Bovine respiratory disease (BRD) caused or complicated by *Mycoplasma bovis* has posed a problem for cattle producers for many decades. The ubiquitous *M. bovis* microbes can work alone or, more often, in concert with a mix of other bacterial and viral pathogens to make cattle underperform, become sick, and die. As a result, *M. bovis* continues as a widespread and insidious problem for beef producers

and veterinarians. Unfortunately, by the time clinical signs of *M. bovis* disease are detected, effective treatment with available antimicrobials may be too late to avoid poor performance, chronic disease, and death losses in calves.⁴

The insidious nature of *M. bovis* and poor response to treatment can be explained by its robust abilities to evade the immune response.⁵⁻⁷ Mycoplasmas have been shown

PROTIVITY™

Key Facts:

- First and only **modified-live** *M. bovis* vaccine, for robust immune response/efficacy.
- Safe for cattle **1 week** of age or older.
- For beef and dairy cattle.
- Flexible and compatible with existing health protocols.
- 2 mL SC in the neck.
- 2 doses, 21 days apart.
- Vials hold 10 or 50 doses.
- Multiple studies confirm safety.
- No injection site reactions observed in safety trials.
- Compatible for use with EXCEDE® (ceftiofur crystalline free acid)/EXCENEL® (ceftiofur hydrochloride)/NAXCEL® (ceftiofur sodium).
- Supported by Zoetis, Veterinary Medical Information and Product Support, Technical Support, Customer Service, and Sales Force.
- Store at 2-8°C (35-46°F).
- Not for use within 21 days before slaughter.

When properly used as part of a complete calf rearing program, including use of other vaccines like INFORCE 3®, and ONE SHOT® BVD, PROTIVITY helps provide for the most comprehensive BRD protection available for young calves.

to modulate the immune system through extensive variation of surface proteins along with unique modulation of the immune response through resistance to monocyte and macrophage phagocytosis, inhibition of peripheral blood mononuclear cell (PBMC) proliferation, modulation of cytokine production, down-regulation of cell-mediated (Th1) and up-regulation of humoral (Th2) CD4 response along with the ability to invade erythrocytes, PBMCs, and epithelial cells.⁵⁻⁷

The unique ability of mycoplasmas to modulate the immune response causes further frustration because few tools exist to consistently prevent or control *M. bovis* and its associated impacts. Killed vaccines (commercial and autogenous) are limited in their ability to stimulate cell-mediated immune responses compared to modified-live vaccines. Until now, some producers have thus resorted to unproven autogenous vaccines that can be difficult to access, are expensive, and also offer limited evidence of effectiveness.^{5,6}

Furthermore, *M. bovis* typically starts impacting the health of calves *early in life*, so the earlier a vaccine protocol can be implemented, the better. Available USDA commercial vaccines are not approved for use in calves less than 45 days of age, thus leaving a wide window for potential disease progression, lung damage, and the potential for a life-long setback for health and productivity. The insidious and often unforeseen impacts of *M. bovis* infections may lead to less optimal cattle health and production, and can tax the reputations of producers and veterinarians striving to produce the highest quality cattle.

PROTIVITY™

PROTIVITY™, a novel cattle vaccine from Zoetis, offers an effective and proactive approach to help control the widespread problem of *M. bovis*, and has provided the cattle industry with a tool for reliable *M. bovis* immunological protection. PROTIVITY is the first **modified-live** *M. bovis* vaccine, and has been shown to help prevent irreversible lung damage due to *M. bovis*. Further, PROTIVITY can be

administered to calves as young as **1 week of age**, providing *M. bovis* protection for calves **earlier** than conventional killed vaccines. This notable feature allows flexibility in the timing and convenience of vaccination while helping provide calves their best start on life.

PROTIVITY is labeled as “*effective for the vaccination of healthy cattle 1 week of age or older against respiratory disease caused by Mycoplasma bovis.*” After aseptically rehydrating the freeze-dried, refrigerated vaccine using the sterile diluent provided, 2 mL should be administered to healthy cattle subcutaneously (SC) in the neck. A second dose should be similarly administered 21 days later.

PROTIVITY represents a technological advance that delivers proven respiratory protection and flexibility for young, vulnerable calves. By adding PROTIVITY to comprehensive health protocols for beef or dairy calves, producers can better equip their cattle for a lifetime of productivity and significantly upgrade prospects for successful BRD management.

Efficacy Research

Study Design

A study assessed the efficacy of PROTIVITY for protecting young vaccinated calves against challenge with a virulent field strain of *M. bovis*.¹ This trial involved 83 healthy young colostrum-deprived Holstein calves (male and female) ranging from 7 to 12 days of age at the start of the study. Calves were randomized into 3 treatment groups including 39 PROTIVITY vaccinated calves, 39 saline controls, and 5 non-vaccinated and non-challenged controls. All calves were seronegative and nasal swab negative for *M. bovis* prior to vaccine administration, given as 2 doses SC, 21 days apart. Calves were also confirmed negative for BVDV persistent infection (PCR on ear notch samples). All these status evaluations were conducted 4 days before study initiation.

Researchers employed a generalized randomized block design throughout the study, with the blocking factor based on order of enrollment and pen location. During

the initial vaccination phase of the study, 78 calves were randomly allotted to 2 treatment groups and housed indoors in 4 group rooms (2 rooms/treatment group), each holding 20 individual pens. Calves in the respective treatment groups were vaccinated on study as follows (Figure 1):

- **Control** (saline), 2 mL SC (n=39);
- **PROTIVITY**, 2 mL SC (n=39).

Animals were observed for post-vaccination reactions within 4 hours of vaccination.

Prior to challenge, treatment groups were commingled within the rooms, and each animal was inoculated with a virulent *M. bovis* challenge isolate of US origin (representing an aggressive respiratory infection). The challenge strain was isolated from a calf with BRD signs and typical *M. bovis* lung lesions on a farm in Kansas.

Five animals were randomly assigned to a negative control group (no vaccine, no challenge), to monitor for any background *M. bovis* infection in the herd by serology, and to confirm pre-challenge baseline levels of lung lesions. Daily clinical observations and recording of rectal temperatures began just prior to challenge and continued through study end. Calves were specifically observed and scored for clinical signs of *M. bovis* disease (pyrexia, respiratory signs: attitude, nasal discharge, respiratory distress). Blood samples were collected at various time points to monitor serological response to *M. bovis* (enzyme-linked immunosorbent assay, ELISA). At the end of the study, all calves were humanely euthanized and necropsied, and lungs were scored for percent of total lung with lesions. Two swabs were also collected from the periphery of a lesion and submitted for bacterial isolation of *M. bovis* and other respiratory pathogens.

Collected data were statistically analyzed according to standard methods, using room as the experimental unit during the vaccination phase, and animal as the experimental unit during the challenge phase. Mitigated fraction was calculated based on lung lesion scores (analysis performed at a *P* value of ≤ 0.05). In addition, the clinical relevance and magnitude of disease reduction was

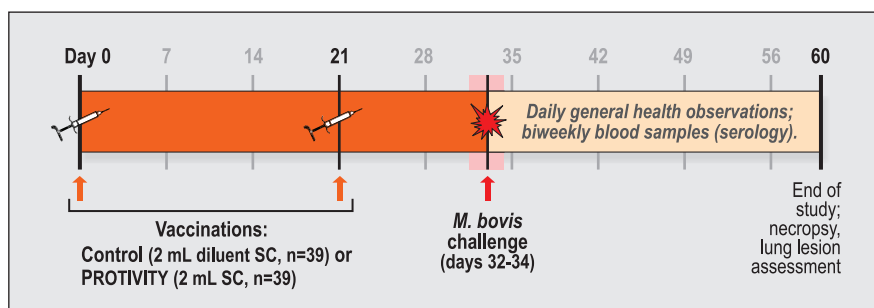


Figure 1 – Study design and timeline.

assessed by utilizing a 5-number summary in comparing the lung lesions for each quartile (minimum, first quartile, median, third quartile, and maximum) of each treatment group. Based on additional analysis done for non-US regulatory agencies, data for other supporting efficacy parameters, such as serology, temperature, and clinical signs, were also statistically analyzed. Personnel performing lab work, conducting clinical observations (during the challenge phase), and scoring lungs for percent lesions were masked to treatment group assignments.

Results

Post challenge, 6 calves (5 controls, 1 vaccinate) were removed for humane reasons prior to the end of the study due to severe clinical disease related to the *M. bovis* challenge. Data from these calves were included in the data analysis.

Study outcomes summarized in Figure 2 show that PROTIVITY vaccination, relative to controls, generated 74% ($P \leq 0.0001$) reduction in the mean percentage of total lung with lesions. The mitigated fraction estimate for the median percentage of total

All study calves were exposed on 3 sequential days with an aerosolized *M. bovis* challenge infection.

Mitigated fraction: relative increase in the probability that disease in a vaccinated animal will be less severe than that in a non-vaccinated animal. Mitigated fraction helps focus attention on the *clinical relevance* of a study outcome.

PROTIVITY vaccinates showed a 74% relative reduction in lung lesions.

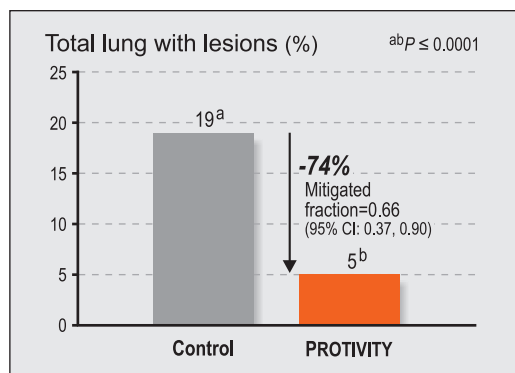


Figure 2 – Post-challenge severity of *M. bovis* lung lesions (least squares means).

Calves vaccinated with PROTIVITY were protected against fever and clinical signs associated with *M. bovis* disease.

lung with lesions was 0.66 (95% CI: 0.37, 0.90) for PROTIVITY vs controls, indicating a clinically relevant reduction in lung lesions in the vaccinated animals. These lung lesion outcomes clearly demonstrated a highly positive vaccine effect for PROTIVITY, and an onset of immunity as soon as 11 days after administration of the second dose.

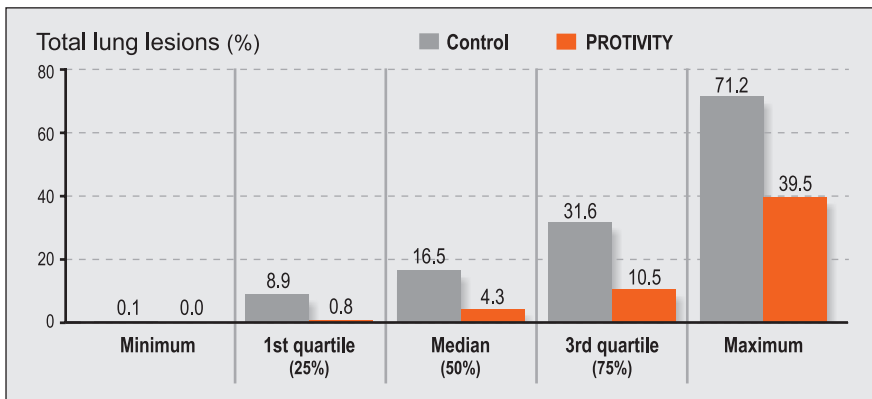


Figure 3 – Five-number summary for percentage of total lung with lesions (least squares means).

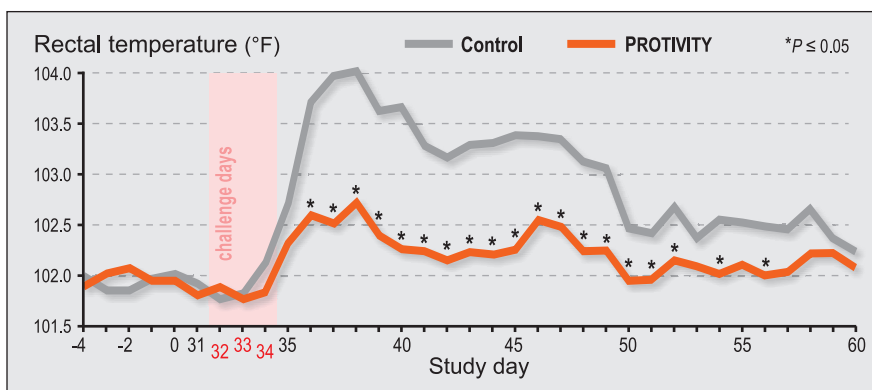


Figure 4 – Rectal temperature outcomes.

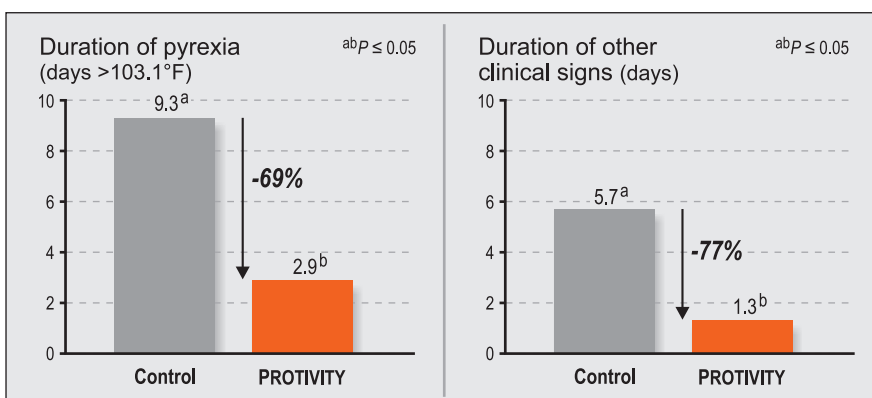


Figure 5 – Comparative duration of fever and other clinical signs (attitude, nasal discharge, and/or respiratory effort) due to *M. bovis* respiratory disease.

The clinical relevance and magnitude of disease reduction efficacy induced by PROTIVITY was further supported by the 5-number summary comparing percentage of total lung with lesions in controls vs vaccinates (Figure 3). This analysis detected favorable shifts in the quartiles between the control and PROTIVITY treatment groups: 1) the 3rd quartile (75th percentile) estimate for PROTIVITY was below the median estimate for controls; and 2) the median estimate for PROTIVITY was below 1st quartile (25th percentile) estimate for controls.

Outcomes from other clinical and serologic parameters assessed during the study for non-US regulatory agencies also demonstrated significant ($P \leq 0.05$) statistical improvements for PROTIVITY vaccinates.⁸

- Mean rectal temperature of the control group was significantly higher than that of the PROTIVITY group on most post-challenge days (Figure 4). Similarly, the duration of pyrexia ($\geq 103.1^\circ\text{F}$) averaged only 2.9 days for vaccinates, significantly shorter (-69%) than the 9.3 days of pyrexia duration in controls (Figure 5).
- Analysis of the duration of at least 1 other clinical sign of *M. bovis* respiratory disease (attitude, nasal discharge, respiratory effort; Figure 5) revealed a significantly shorter duration (-77%) in PROTIVITY vaccinates (1.3 days) compared to control animals (5.7 days).
- Serological responses to vaccination and challenge were significantly greater in PROTIVITY vaccinates (Figure 6), demonstrating an anamnestic response.

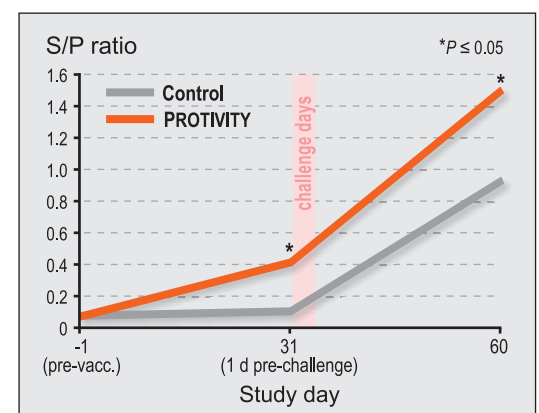


Figure 6 – Serologic responses before and after *M. bovis* challenge (ELISA titers).

The study was deemed valid because:

- 1) All animals enrolled were sero-negative prior to vaccination and their respective naso-pharyngeal swabs were negative for *M. bovis*, indicating they were susceptible to *M. bovis*;
- 2) Control calves were sero-negative prior to challenge;
- 3) Pre-challenge lung lesion scores of the negative control animals were not $\geq 5\%$ on day 31;
- 4) The median percent of post-challenge total lung with lesions in controls was $>5\%$, indicating a clinically relevant level of disease.

Colostrum-deprived calves were used in this study to avoid interference by maternal antibodies when testing for vaccine efficacy. Mild lameness (joint ill) observed in a few calves was typical for colostrum-deprived calves and occurred in both treatment groups. Treatment with procaine penicillin G (which has no antibacterial activity against *M. bovis*) resolved lameness signs, indicating the cases were not due to *M. bovis* vaccination.

Conclusions

This study involving neonatal calves demonstrated the clinical efficacy of PROTIVITY against respiratory disease caused by *M. bovis*, even in the face of a very aggressive challenge infection. The incidence of animals with clinically relevant lung lesions was significantly reduced 74%. In addition, young calves vaccinated with PROTIVITY were protected against elevated temperatures and clinical signs typically associated with *M. bovis* acute respiratory disease, and vaccination generated antibody responses significantly higher and earlier than controls.

The efficacy of the 2-dose PROTIVITY regimen was firmly established and provided substantial evidence that supported USDA licensing of this novel modified-live product. Furthermore, an onset of immunity as soon as 11 days after administration of the second dose was demonstrated. PROTIVITY is an effective vaccine for *M. bovis* respiratory disease in young calves and represents a valuable addition to comprehensive management protocols aimed at optimizing herd health, productivity, and profitability.

Safety Research

Multiple safety studies were conducted in support of PROTIVITY licensing.

Field Safety Study 1 (8 weeks)

Study Design

A multi-location field study evaluated the safety of vaccination with PROTIVITY when administered to 1069 young, healthy calves maintained under typical commercial production conditions at sites in California (n=357), Idaho (n=359), and Kansas (n=353).² The CA facility represented a large and intensive calf-rearing business where the neonatal population was expected to be highly stressed. Each day the operation received 500 to 1000 head of day-old dairy calves from local farms, managing over 200,000 head/year. The ID site represented a typical dairy operation and the KS site represented a beef cow-calf operation. Test animals comprised both beef and dairy breeds (33% Angus cross, 67% Holstein; 52% male, 48% female), were maintained in individual hutches (CA and ID) or open pasture (KS), and were split into 2 approximate age categories:

- 1) **week-old** (1-8 days of age, mean ~5 days; n=536, all of the CA calves and half of the ID calves);
- 2) **month-old** (25-43 days of age, mean ~31 days; n=533, all of the KS calves and half of the ID calves).

Animals were assigned to 2 vaccination treatment groups (2:1 vaccinate:control ratio) according to a general randomized block design, with blocks based on order of enrollment within each age group within each pen/pasture at each site. Calves in

Two field studies were conducted in young calves to determine the safety profile of PROTIVITY.

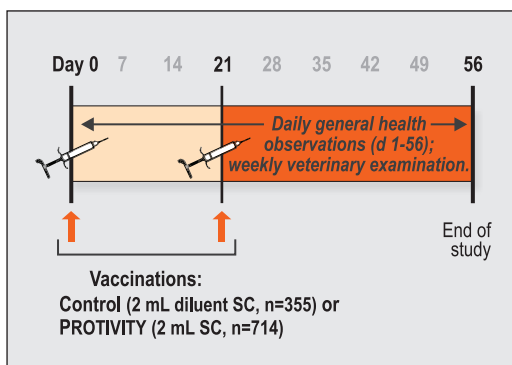


Figure 7 – Study design and time line (1069 Angus or Holstein calves across 3 sites, 1-43 days of age at study day-0).

The rate of vaccinated calves that exhibited an abnormal event was similar to that of controls, showing no increased risk for cattle vaccinated with PROTIVITY.

The majority of all abnormal health events in vaccinated animals resolved and were unrelated to the product.

The 8-week, multi-site field study demonstrated the safety of PROTIVITY in young calves, including those only a week old at vaccination.

the respective treatment groups were vaccinated on study days 0 and 21 as follows (Figure 7):

- **Control** (inert diluent), 2 mL SC (n=355);
- **PROTIVITY**, 2 mL SC (n=714).

Day-0 injections were administered on the left side of the neck, and day-21 on the right side. Antimicrobials with potential impact on *M. bovis* were not used prior to or following vaccination.

Animals were observed for at least 4 hours after each vaccination for any local or systemic reactions. Animals were also visually observed for injection site reactions for 3 weeks after each vaccination. General health observations for abnormal events were performed daily for 56 days, and each individual animal was more closely evaluated weekly by a study veterinarian. Sick or moribund animals were treated or euthanized as recommended by attending veterinarians. Standard farm husbandry activities (vaccinations, standard treatments) could proceed while calves were on test, except for use of antimicrobials with *M. bovis* activity or anti-inflammatories. If an abnormal health event involved lameness and required euthanization, culture and pathological examination of synovial fluids and lung lesions were performed at necropsy for evidence of *M. bovis* involvement.

Data regarding abnormal health events were summarized for each animal by treatment and time-point. The number and percentage of animals having an abnormal health observation were reported for each treatment and age category.

Results

Few reactions were observed within 4 hours of vaccine or diluent administrations. After the first vaccination at the CA site, 2 control calves appeared depressed and 1 vaccinee had rapid breathing, but all issues resolved by the following day without treatment. No local or systemic reactions were observed in any calf following the second vaccination, and no injection site reactions were observed at any time.

Over 300 abnormal health events were observed during the study, with the incidence, types, and proportions of the

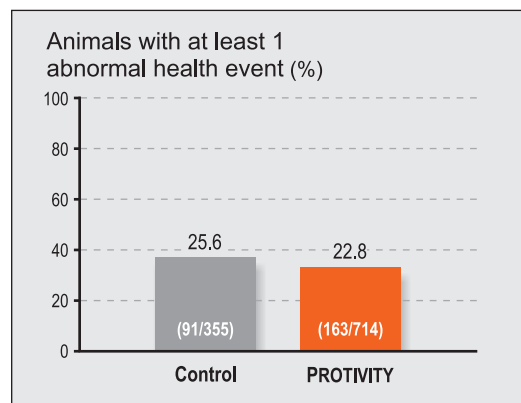


Figure 8 – Equitable low rate of abnormal health events in controls and vaccinees of 8-week safety study 1.

events distributed similarly among controls and vaccinees. The rate of calves exhibiting 1 or more abnormal events was 25.6% for controls and 22.8% for vaccinees (Figure 8), showing no increased incidence for the PROTIVITY group. The large majority of the abnormal events (322; 93%) occurred in 233 of the week-old calves and involved cases of diarrhea, pneumonia, and rapid breathing, health issues commonly afflicting neonatal calves. As expected, most cases were observed at the CA site, an intensive dairy calf-management operation with challenging conditions for young, highly stressed calves. Far fewer abnormal health events (23; 7%) occurred in month-old animals and were consistent with the type of animals and site management practices.

Across the 714 animals vaccinated twice with PROTIVITY, only 1 week-old calf (0.14% of vaccinees) demonstrated an abnormal health event that might have been related to the vaccine. This single animal at the CA site developed pneumonia, then lameness, and was treated with ceftiofur, thereby resolving the pneumonia and possibly any infectious pathogens in the joint that were susceptible to ceftiofur, but not the lameness. The animal was euthanized and diagnostic necropsy revealed a carpal joint with gross abnormalities (cloudy joint fluid). Mycoplasmal organisms were detected in joint fluid, with PCR and genomic sequencing confirming the presence of the *M. bovis* vaccine strain. However, researchers could not determine whether the lameness was caused solely by the *M. bovis* strain, or if bacterial pathogens related to the

pneumonic illness might have predisposed the calf to lameness. This latter scenario could not be dismissed since bacterial pathogens may have been cleared from the affected joint by the antimicrobial therapy.

Overall, the types and frequencies of abnormal health events observed during the study were consistent with expectations typical for the ages and breeds of calves under study, and the types of management systems employed.

Conclusions

This 8-week, multi-site field study demonstrated the safety of PROTIVITY in young calves, including those only a week old at the time of vaccination. The types and frequencies of abnormal health events observed at all 3 sites were within normal expected ranges, even under intense calf-rearing management conditions. The majority of all abnormal health events in vaccinated animals resolved and were unrelated to the product.

Field Safety Study 2 (4 months)

Study Design

A trial was conducted to evaluate longer-term safety impacts of vaccination with PROTIVITY when administered to week-old, conventionally raised calves maintained under typical commercial production conditions over a 4-month period.³

The study involved 148 healthy Holstein or Holstein-cross neonatal calves averaging 5.7 days of age on day-0 (range 4-7 days; 52% male, 48% female), housed in individual outdoor calf hutches after arrival at a research farm in Michigan. All animals were negative for persistent BVDV infection (ear notch), free of concurrent disease, and received antimicrobials, vaccines, and other pre-treatments according to normal husbandry practices at the farm. Calves were assigned to 1 of 2 vaccination treatment groups (2:1 vaccine:control ratio) according to a general randomized block design, with blocks based on hutch location. Calves in the respective treatment groups were vaccinated on study days 0 and 21 as follows (Figure 9):

- **Control** (inert diluent), 2 mL SC (n=51);
- **PROTIVITY**, 2 mL SC (n=97).

Day-0 injections were administered on the left side of the neck, and day-21 on the right side. Antimicrobials with impact on *M. bovis* were not used prior to or following vaccination.

Animals were observed for at least 4 hours after each vaccination for any local or systemic reactions. General health observations for abnormal events were performed daily for 120 days, and each individual animal was more closely evaluated weekly by a study veterinarian. Deep nasal swabs were collected from each animal on day -1 and every 2 weeks thereafter (days 14, 28, 42, 56) until each calf had 2 consecutive samples negative for *M. bovis* by bacterial culture following the second vaccination. After day-60, weaned calves were moved from hutches and commingled across 5 identical pastures (n=30/pasture, 10 blocks).

Sick or moribund animals were treated or euthanized as recommended by attending veterinarians. If an abnormal health event involved non-resolving lameness and required euthanization, culture and pathological examination of synovial fluids and lung lesions were performed for evidence of *M. bovis* involvement.

All personnel performing clinical observations and laboratory assays were masked to treatment group assignments. Data regarding abnormal health events were summarized for each animal by treatment and time-point. The number and percentage of animals with an abnormal health observation were reported for each treatment.

The safety impacts of PROTIVITY vaccination in week-old calves were evaluated over a 4-month period.

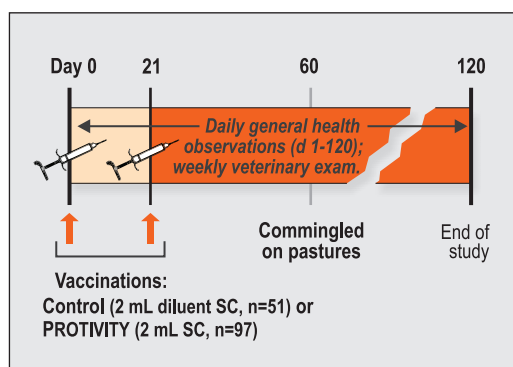


Figure 9 – Study design and time line (148 Holstein calves, 4-7 days of age at study day-0).

Abnormal events occurred at similar rates for both vaccinates and controls, and none were related to PROTIVITY.

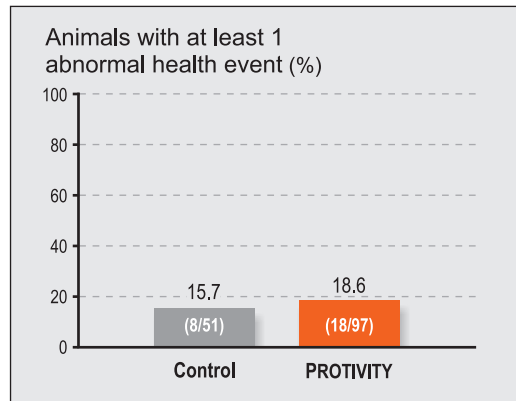


Figure 10 – Equitable low rates of abnormal health events in controls and vaccinates observed over the 4-month period during safety study 2.

Results

No local or systemic reactions were observed in any calf within 4 hours of vaccine administrations, and no injection site reactions were observed at any time.

A total of 32 abnormal health events occurring across 26 animals were observed during the study. Thus, a majority of abnormal events were from calves that had a single event and recovered. Animals affected by abnormal events occurred at similar rates across both treatment groups: 15.7% of controls and 18.6% of vaccinates (Figure 10). Notably, *none of the abnormal events were related to PROTIVITY.*

Abnormal health events noted during the study included colitis, cough, diarrhea, eye disorders, lethargy, palpable lumps on jaws, respiratory disorder, and bloat. One control animal was humanely euthanized on day-107 and necropsy determined bloat/overeating as the cause of death (no mycoplasmas or any other bacterial pathogens found in lungs, trachea, or joints). Mass treatment of cattle on 3 of the 5 pastures was deemed necessary at 3 to 4 weeks after commingling for treatment of mild respiratory disease (signs included mild nasal discharge and cough). All animals on the 3 pastures were treated with 3 days of ceftiofur (which lacks *M. bovis* activity) and all animals recovered with no issues.

This longer duration study further confirmed the safety of PROTIVITY in young calves.

M. bovis was never isolated from cultures of any deep nasal swabs at anytime during the study (100% negative), confirming the absence of target pathogens that might confound a safety study.

Conclusions

Outcomes of this longer-term study further confirmed the safety of PROTIVITY in young (week-old) calves. No unexpected events or increased frequency of abnormal events were detected during 4 months of post-vaccination clinical observation. All abnormal health events noted in vaccinated animals resolved and were unrelated to PROTIVITY. Furthermore, no lameness was observed throughout the study period, and *M. bovis* was never recovered in any of the deep nasal swabs. These safety studies demonstrate that PROTIVITY is a safe vaccine for use in young calves.

Implications

PROTIVITY is a safe and effective vaccine for *M. bovis* respiratory disease in young calves, and represents a valuable addition to comprehensive management protocols aimed at optimizing herd health, productivity, and profitability.

- PROTIVITY is the first modified live *M. bovis* vaccine with USDA approval and validation of efficacy and safety in healthy calves as young as 1 week of age.
- In concert with vaccines for other respiratory pathogens, PROTIVITY offers a proactive approach to a widespread problem (*M. bovis*), and provides another tool for BRD prevention/control and innovative BRD management.
- The modified-live PROTIVITY formulation is an effective alternative to unproven autogenous vaccines and commercial killed vaccines. These studies offer evidence that PROTIVITY mitigates the incidence and severity of *M. bovis* pneumonia and is safe to use in calves as young as 1 week of age.
- PROTIVITY can be administered to calves as young as 1 week of age, allowing flexible use that can likely fit most vaccination schedules.

- PROTIVITY can be used with EXCEDE® (ceftiofur crystalline free acid)/EXCENEL® (ceftiofur hydrochloride)/NAXCEL® (ceftiofur sodium) if antimicrobial therapy is needed prior to or during the immune-response phase after vaccination, since these antimicrobial products will not impact the replication of protective mycoplasmal microbes in the vaccine.
- Widespread adoption of PROTIVITY may help reduce industry use of antimicrobials for BRD treatment through decreased incidence and severity of *M. bovis* pneumonia, resulting in a decreased need for antimicrobial therapy and potentially less antimicrobial resistance.

The mitigating effect of a lower incidence of *M. bovis* pneumonia can result in less use of antimicrobial treatments, potentially contributing to less antibiotic resistance.

Conclusions

An extensive study demonstrated the efficacy of PROTIVITY for protecting young vaccinated calves against challenge with a virulent field strain of *M. bovis*. The safety of PROTIVITY was also rigorously evaluated (especially in young calves).

PROTIVITY is effective and safe for vaccination of cattle 1 week of age or older against *M. bovis* respiratory disease, and represents a technological advance for veterinarians and beef producers who want to upgrade their management of respiratory disease and help improve the health, productivity, and profitability of their cattle.

PROTIVITY represents a valuable upgrade to management protocols aimed at optimizing herd health, productivity, and profitability.

IMPORTANT SAFETY INFORMATION:

EXCEDE: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCEDE. EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the β -lactam group (penicillins and cephalosporins) of antimicrobials. Inadvertent intra-arterial injection is possible and fatal. Do not use in calves to be processed for veal. Pre-slaughter withdrawal time is 13 days following the last dose. See full Prescribing Information.

EXCENEL RTU EZ: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCENEL RTU EZ. Do not use in animals found to be hypersensitive to the product. Do not slaughter cattle for 4 days following last treatment. Do not use in calves to be processed for veal. See full Prescribing Information.

NAXCEL: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to NAXCEL. NAXCEL has a pre-slaughter withdrawal time of four days. Do not use in animals found to be hypersensitive to the product. See full Prescribing Information.



For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle. Not for use in calves to be processed for veal.

CAUTION

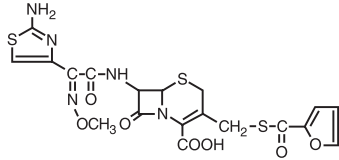
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including β -lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a caprylic/capric triglyceride and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:

7-[[[2-(2-Amino-4-thiazolyl)-2-(methoxymino)acetyl]amino]-3-[[[2-(furan-2-carbonyl)thio]methyl]-9-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

INDICATIONS

EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD), shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levi* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for treatment of acute metritis (0-10 days post-partum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle.

DOSAGE

Treatment of BRD and bovine foot rot

Administer as a single subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to cattle at a dosage of 3.0 mg ceftiofur equivalents (CE)/lb (6.6 mg CE/kg) body weight (BW) (1.5 mL sterile suspension per 100 lb BW).

In beef and non-lactating dairy cattle, EXCEDE Sterile Suspension may also be administered as a single subcutaneous injection in the middle third of the posterior aspect of the ear at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

Most animals will respond to treatment within three to five days. If no improvement is observed, the diagnosis should be reevaluated.

Control of BRD

Administer as a subcutaneous injection either in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) to beef and non-lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

Clinical studies indicate that administration of EXCEDE Sterile Suspension is effective for the control of respiratory disease in beef and non-lactating dairy cattle at "high risk" of developing BRD. One or more of the following factors typically characterize calves on arrival at high risk of developing BRD.

- Cattle are from multiple farm origins,
- cattle have had extended transport times (that may have included few if any rest stops),
- ambient temperature change from origin to arrival of 30° F or more,
- cattle have had continued exposure to extremely wet or cold weather conditions,
- cattle have experienced excessive shrink or excessive arrival processing procedures (such as castration, dehorning).

Treatment of Acute Metritis

Administer as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW). Repeat this dose in the contra-lateral (opposite) ear approximately 72 hours following the initial dose.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

Weight (lb)	Dose Volume (mL)	Weight (lb)	Dose Volume (mL)
100	1.5	1100	16.5
200	3.0	1200	18.0
300	4.5	1300	19.5
400	6.0	1400	21.0
500	7.5	1500	22.5
600	9.0	1600	24.0
700	10.5	1700	25.5
800	12.0	1800	27.0
900	13.5	1900	28.5
1000	15.0	2000	30.0

ADMINISTRATION

ADMINISTRATION FOR THE MIDDLE THIRD OF THE EAR

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior ear of cattle.
- Deposit as a single subcutaneous injection in the middle third of the posterior aspect of the ear, avoiding all blood vessels. See Figures 2 and 3.
- Adjust the needle insertion point to avoid any blood vessels, previous implants, ear tags or ear tag holes. Do not administer intra-arterially.
- Deliver the entire contents of the syringe.
- When administered correctly, a subcutaneous bleb of EXCEDE Sterile Suspension will appear.
- When withdrawing the needle, apply pressure to the needle insertion point, and massage toward the base of the ear.

Figure 2. Subcutaneous administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear.

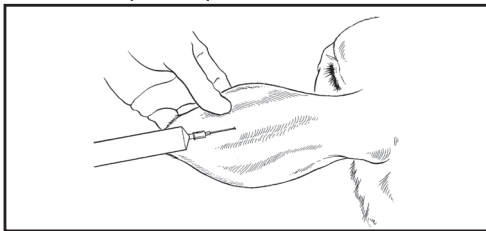
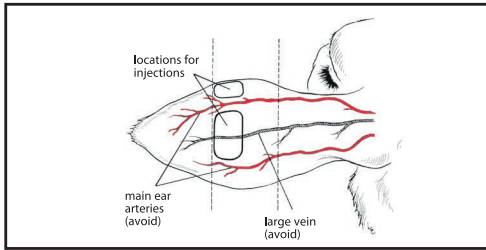


Figure 3. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.



ADMINISTRATION FOR BASE OF THE EAR

In lactating dairy cattle the injection techniques for subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) can be made by the rostral or ventral injection techniques.

In beef and non-lactating dairy cattle the SC injection in the base of the ear can be made by the rostral, ventral or toward the opposite eye injection techniques.

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior aspect of the ear where it attaches to the head (base of the ear).
- The subcutaneous (SC) injection may be made using the toward the opposite eye, rostral, or ventral techniques. Hold the syringe and needle and insert the needle as described below.
- Deliver the entire contents of the syringe.
- Do not administer EXCEDE Sterile Suspension in the neck.

Administration for the Base of the Ear: Toward the Opposite Eye Technique

- Hold the syringe and needle behind the ear to be dosed 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 Figures 4 and 5.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining this angle. See Figure 4.

Figure 4. Subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).

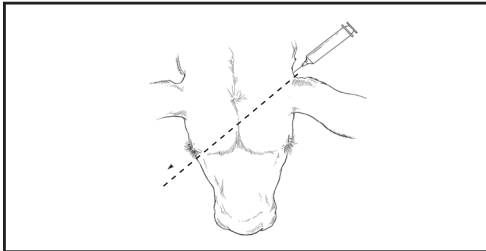
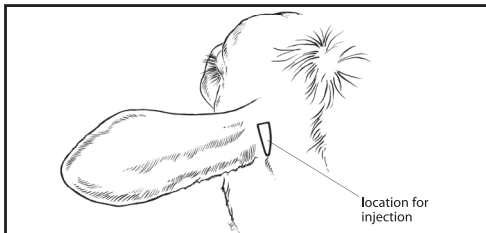


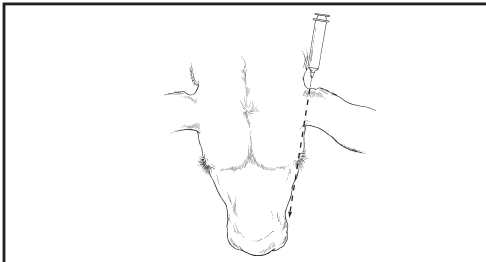
Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).



Administration for the Base of Ear: Toward the Same Eye Technique or Rostral Direction

- Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the eye on the same side of the head. See Figures 5 and 6.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining the needle position. See Figure 6.

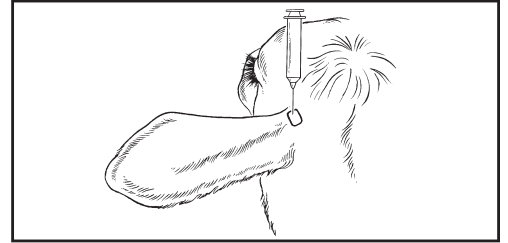
Figure 6. Diagram of head showing the direction for the base of ear injections administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.



Administration for Base of the Ear: Ventral Technique

- Hold the syringe and needle above the ear to be dosed so that the needle and syringe are pointing ventrally toward the base of the ear. The needle will be inserted into the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while pointing ventrally. Care should be taken to not insert the needle through the cartilage of the ear. See Figure 7.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining needle position. See Figure 7.

Figure 7. Diagram of head showing the direction of base of ear injections when administered ventrally into the loose skin in the caudal aspect of the base of the ear.



CONTRAINDICATIONS

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet or to report any adverse event please call 1-888-963-8471.

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed towards the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal.

RESIDUE WARNINGS

- **Following label use as either a single-dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last treatment.**
- **Following label use as either a single-dose or 2-dose regimen, no milk discard period is required for this product.**
- **Use of dosages in excess of 3.0 mg CE/lb (6.6 mg CE/kg) BW or administration by unapproved routes (subcutaneous injection in the neck or intramuscular injection) may cause violative residues.**
- **A withdrawal period has not been established for this product in pre-ruminating calves.**
- **Do not use in calves to be processed for veal.**

ANTIBACTERIAL WARNINGS

Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant bacteria.

PRECAUTIONS

Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Following injection in the posterior aspect of the ear where it attaches to the head (base of the ear), areas of discoloration and signs of inflammation may persist at least 13 days post administration resulting in trim loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle.

The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed towards the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal. During the conduct of clinical studies, there was a low incidence of acute death (see ANIMAL SAFETY) confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

CLINICAL PHARMACOLOGY

Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, MOE) of beef and non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear, BOE) of beef, non-lactating dairy, and lactating dairy cattle, provides therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC₉₀) for the labeled BRD pathogens, *Pasteurella multocida*, *Mannheimia haemolytica* and *Histophilus somni*, for generally not less than 150 hours after a single administration (See Figure 8).

Single Dose Regimen

The pharmacokinetic parameters for the two subcutaneous locations of injection (MOE and BOE) are found in Table 2. Statistical analyses of the data from these two subcutaneous injection sites (MOE and BOE) demonstrate that they are therapeutically equivalent.

Figure 8. Average (n=12/group) plasma concentrations of ceftiofur and desfuryleftiofur-related metabolites after administration of EXCEDE Sterile Suspension at 3.0 mg CE/lb (6.6 mg CE/kg) BW via subcutaneous injection into one of two different locations of the ear, middle third of the ear (MOE Cattle) and base of the ear (BOE Cattle) in beef cattle as well in the base of the ear (BOE Lactating) in lactating dairy cattle.

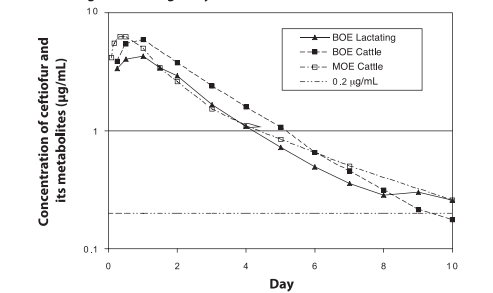


Table 2. Average (n = 12/group) pharmacokinetic parameters for ceftiofur and desfuryleftiofur metabolites calculated after a single subcutaneous administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension in either the middle third of the ear or the base of the ear.

Pharmacokinetic Parameter	Beef - Middle Third of the Ear Mean Value ± Standard Deviation	Beef - Base of the Ear Mean Value ± Standard Deviation	Dairy Cow - Base of the Ear Mean Value ± Standard Deviation
C _{max} (µg CE/mL)	6.90 ± 2.68	6.39 ± 1.79	4.44 ± 1.65
t _{max} (h)	12.0 ± 6.2	19.8 ± 5.81	19.00 ± 8.02
AUC ₀₋₁₀₀ (µg·h/mL)	376 ± 66.1	412 ± 67.3	313 ± 85.5
t _{0.5, model} (h)	183 ± 40.8	NE	NE
t _{0.5, no3} (h)	246 ± 48.5	218 ± 45.5	205 ± 35.7
t _{1/2} (h)	62.3 ± 13.5	40.7 ± 11.2	43.92 ± 9.84

C_{max} (µg CE/mL) = maximum plasma concentration (in µg CE/mL).
t_{max} (h) = the time after injection when C_{max} occurs (in hours).
AUC₀₋₁₀₀ (µg·h/mL) = the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg CE/mL).
t_{0.5, model} (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using compartmental pharmacokinetic techniques.
t_{0.5, no3} (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using noncompartmental pharmacokinetic techniques.
t_{1/2} (h) = terminal phase biological half life (in hours)
NE = Not estimated

Two-Dose Regimen

A two-dose regimen of 6.6 mg CE/kg BW administered 72 hours apart is required for the treatment of acute metritis in lactating cows. The mean plasma concentration vs. time profile for ceftiofur and desfuryleftiofur-related metabolites for the 2-dose regimen in 12 cows is shown in Figure 9 below. The pharmacokinetic parameters for the 2-dose regimen are provided in Table 3.

Figure 9. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcutaneous Injections of EXCEDE 72 hours apart at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW in 12 lactating cows.

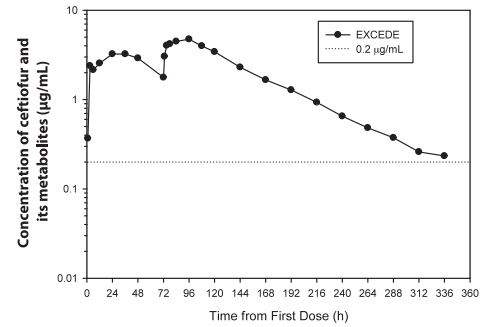


Table 3. Average (n = 12) Pharmacokinetic Parameters Following Two Subcutaneous Injections of EXCEDE Sterile Suspension at a Dose 3.0 mg CE/lb (6.6 mg CE/kg) BW at a 72 Hour Interval.

PK Parameter	Mean ± Standard Deviation
AUC ₀₋₁₀₀ (µg·h/mL)	651 ± 119
t _{max} (h)	55.7 ± 4.84
t _{0.5} (h)	341 ± 34.0
T _{max} (h)	77.1 ± 33.4
C _{max} (µg/mL)	5.98 ± 2.51

MICROBIOLOGY

Ceftiofur has demonstrated *in vitro* activity against *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, three major pathogens associated with BRD, and against *Fusobacterium necrophorum* and *Porphyromonas levi* associated with bovine foot rot.

A summary of the susceptibility of BRD and foot rot pathogens is presented in Table 4. BRD isolates were obtained from cattle enrolled in a field study conducted in the United States that were diagnosed with BRD. Foot rot isolates were obtained from cattle enrolled in a field study conducted in the United States and Canada that were diagnosed with foot rot. Susceptibility testing was conducted according to the Clinical and Laboratory Standards Institute (CLSI) M7-A3 and M11-A6 standards for BRD and foot rot isolates, respectively.

Table 4. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from cattle with naturally occurring BRD or foot rot.

Indicated pathogen	Year of isolation	Number of isolates	MIC ₅₀ ** (µg/mL)	MIC ₉₀ ** (µg/mL)	MIC range (µg/mL)
<i>Mannheimia haemolytica</i>	1996 to 1997	75	0.008	0.015	0.001 to 0.015
<i>Pasteurella multocida</i>	1996 to 1997	43	0.004	0.004	0.001 to 0.015
<i>Histophilus somni</i>	1996 to 1997	11	0.004	0.004	0.002 to 0.015
<i>Fusobacterium necrophorum</i>	2006 to 2007	148	≤ 0.25	0.5	≤ 0.25 to >128
<i>Porphyromonas levi</i>	2006 to 2007	141	≤ 0.25	2.0	≤ 0.25 to 16

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in cattle after a single administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW and the MIC and susceptibility data, the following breakpoints are recommended for BRD pathogens by CLSI.

Table 5. CLSI-accepted interpretive criteria* for ceftiofur against cattle respiratory pathogens.

Pathogen	Disk potency	Zone diameter (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
<i>Mannheimia haemolytica</i>	30 µg	≥ 21	18 to 20	≤ 17	≤ 2.0	4.0	≥ 8.0
<i>Pasteurella multocida</i>							
<i>Histophilus somni</i>							
S – Susceptible							
I – Intermediate							
R – Resistant							

* These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility. Interpretive criteria for bovine foot rot pathogens have not been established.

EFFECTIVENESS

A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2.0 and 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW for the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously in the middle third of the posterior aspect of the ear. Cattle were clinically evaluated on Days 2 to 4, 14 and 28 and were observed on all other study days. The 3.0 mg CE/lb (6.6 mg CE/kg) BW EXCEDE Sterile Suspension dose significantly (p ≤ 0.05) increased Day 14 treatment success rate, defined as animals that did not require any ancillary treatment and had a rectal temperature of <104°F, normal respiration index, and had no or mild depression on that day.

The effectiveness of a single dose of EXCEDE Sterile Suspension for the control of BRD in feedlot cattle was evaluated in a nine-location field effectiveness study. In addition to standard processing on arrival at feedlots, cattle (n=3911) considered to be at high risk for BRD were assigned to one of four arrival treatments, including EXCEDE Sterile Suspension at 2.0 or 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW or negative control. Effectiveness evaluation was based on the incidence of clinical BRD within 28 days following arrival processing. Administration of a single dose of EXCEDE Sterile Suspension administered subcutaneously in the middle third of the posterior aspect of the ear at arrival processing significantly reduced the incidence of BRD in high-risk feedlot cattle in the 28-day period after arrival processing compared to negative controls.

Base of the ear administration (beef and non-lactating dairy cattle) and middle third of the ear administration (lactating dairy cattle) were compared to the middle third of the ear pharmacokinetic data for beef and non-lactating dairy cattle and were found to be therapeutically equivalent.

The effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a six-location field effectiveness study. Cattle diagnosed with bovine foot rot were enrolled and treated with EXCEDE Sterile Suspension, administered by subcutaneous injection in the base of the ear as a single dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW or an equivalent volume of a vehicle control. Cattle were clinically evaluated 7 days post-treatment for treatment success, which was based on defined decreases in lesion, swelling and lameness scores. A total of 169 beef and dairy cattle were included in the analysis. There was a statistically significant difference (p = 0.0054) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

The effectiveness of EXCEDE Sterile Suspension for the treatment of acute metritis was evaluated in a 15-location field effectiveness study. A total of 1023 cows with a fetid vaginal discharge and a rectal temperature of ≥ 103 °F were enrolled in the study and treated with either a two-dose regimen of EXCEDE (6.6 mg CE/BW) or an equivalent volume of vehicle control, administered approximately 72 hours apart at the base of opposite ears. At 14 days post-treatment, each cow remaining in the study was examined and rectal temperature and vaginal discharge score were recorded. Cows with a non-fetid discharge, and a rectal temperature < 103 °F, and that did not require alternate ("escape") therapy during the 14-day observation period were classified as a cure. The cure rate was significantly higher (p < 0.0001) in EXCEDE-treated cows (362/493, 73.3%) than in vehicle-treated cows (271/489, 55.3%). One cow died 15 to 20 minutes after the second administration of EXCEDE. Necropsy findings determined the probable cause of death to be intra-arterial injection.

ANIMAL SAFETY

Systemic Safety Studies

After parenteral administration, ceftiofur crystalline free acid (as EXCEDE Sterile Suspension), ceftiofur sodium and ceftiofur hydrochloride are rapidly metabolized to desfuryleftiofur. Therefore, studies conducted with ceftiofur sodium are adequate to evaluate the systemic safety of EXCEDE Sterile Suspension. Results from a five-day tolerance study conducted with ceftiofur sodium in normal feeder calves indicated that ceftiofur was well tolerated at 25 mg CE/lb/day for five consecutive days, approximately 8 times the approved dose of EXCEDE Sterile Suspension 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur administered parenterally had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered ceftiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 or 10 mg CE/lb/day then, evaluating up to 3.3 times the approved dose of EXCEDE Sterile Suspension of 3.0 mg CE/lb/day (6.6 mg CE/kg) BW. There were no adverse systemic effects, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder calves. Local tissue tolerance to subcutaneous injection of EXCEDE Sterile Suspension in the posterior ear of cattle was evaluated in a separate study.

The systemic safety of ceftiofur concentrations resulting from product administration at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus middle third of the ear). Based upon the results of this relative bioavailability study, it was determined that the two routes of administration are therapeutically equivalent.

To support systemic target animal safety for the 2-dose metritis regimen, five projected daily doses of NAXCEL Sterile Powder (ceftiofur sodium) at 2.2 mg/kg BW were compared pharmacokinetically with EXCEDE administered 2 times at a 72 hour interval at 6.6 mg/kg BW. The peak concentration (C_{max}) and the extent of exposure (AUC) after two doses of EXCEDE were statistically no higher than the exposure following five daily doses of NAXCEL Sterile Powder in beef cattle.

Investigation of Intra-Arterial and Intravenous Injection

In approximately 6000 animals enrolled in the BRD clinical studies, nine animals died following injection of EXCEDE Sterile Suspension. All deaths were within 30 minutes of the time of injection. The exact cause was confirmed in three animals. These deaths resulted from inadvertent intra-arterial injection of this oil-based suspension into one of the two major auricular (ear) arteries. Intra-arterial injection at this location resulted in direct administration of the oil-based formulation into the arterial blood supply of the brain resulting in embolism and death.

Since intra-arterial injection was confirmed in three animals that died following injection of EXCEDE Sterile Suspension, the consequences of purposeful intra-arterial injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Two heifers (body weight approximately 225 kg) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the middle auricular artery. Both heifers collapsed immediately and died within approximately eight minutes of injection. Intra-arterial injection of EXCEDE Sterile Suspension in the ear will result in death and must be avoided.

Since subcutaneous injection in the ear may potentially result in inadvertent intravenous administration of an injectable product, the consequences of purposeful intravenous injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Three heifers and three steers (body weight range 197-223 kg) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the jugular vein and were monitored for adverse effects following injection. One steer and one heifer had transient (2 to 5 minutes) increases in heart rate without any other untoward signs in these or the other cattle. Intravenous injection of EXCEDE Sterile Suspension is an unacceptable route of administration.

Safety Studies in Beef Cattle

Middle of the ear injection:

A study was designed and conducted to specifically address tissue tolerance in cattle when EXCEDE Sterile Suspension was administered as a single subcutaneous injection into the posterior aspect of the ear of cattle at the recommended dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Results from this study indicate that the subcutaneous injection of EXCEDE Sterile Suspension into the middle third of the posterior aspect of the ear of cattle is well tolerated and characterized by a biphasic thickening of the ear. The initial increase in thickness is attributed to the space required for the volume of injected material. Additional increases in thickness were observed through Day 14 after injection. After Day 14, post injection ear thickness decreased in all animals. One animal carried an injected ear in a drooping position for 7 days post injection. At necropsy, subcutaneous areas of discoloration and some foci of hemorrhage were observed in ears of injected cattle. The discoloration was markedly reduced in size by the end of the study. Ears are inedible tissues in the US (9 CFR 301.2). No signs of irritation were observed on the edible portions of the carcass around the site of the ear.

The local tolerance of the ear of cattle to a single subcutaneous injection of EXCEDE Sterile Suspension was also evaluated in a large multi-location effectiveness study. None of the 1927 animals treated with EXCEDE Sterile Suspension were removed from this trial due to ear irritation although swelling was noted at some injection sites. Leak back and/or bleeding from the injection site was observed in a small fraction of the treated animals immediately after administration. It was concluded that administration of EXCEDE Sterile Suspension in the posterior aspect of the ear was well tolerated and was acceptable under feedlot conditions.

A study evaluated the 56-day feedlot performance of beef steers administered EXCEDE Sterile Suspension alone, EXCEDE Sterile Suspension with a growth promoting implant, growth promoting implant alone, or neither product in a total of 207 Angus and Angus cross-bred steers. The administration of EXCEDE Sterile Suspension in the posterior aspect of the ear with or without growth promoting implants was well tolerated by cattle and did not adversely affect feedlot cattle performance. Based upon the results of this study, the location of implants administered after EXCEDE Sterile Suspension may need to be adjusted slightly within the boundaries of the middle third of the ear in some animals.

Base of the ear injection:

The local tolerance of the ear to a single subcutaneous injection at the base of the ear of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 2926 beef cattle. Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 99.8% of cattle. No post injection problems (excessive bleeding or leak back) were observed in 99.8% of cattle. On Days 28 and 56 post-injection, 97.8% and 98.9% of the cattle had "normal" (no observed swelling) ears.

In a residue study, 72 beef cattle were injected in the base of the ear with EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Injection sites were observed daily from treatment to necropsy (4, 7, 10, or 13 days post-injection) for swelling and drooping, and evaluated grossly at necropsy, using skinning and trimming procedures similar to slaughterhouse practices. All animals had injection site swelling during the study; swelling resolved prior to euthanasia in 23 of 72 animals. None of the animals showed ear drooping. At necropsy, signs of inflammation (hemorrhage, congestion, and firmness of tissue) and presence of drug material were seen in the area around the injection site and on the carcass. At 13 days post-injection, gross lesions were found in the inedible portions of the base of the ear in 18 animals, and in the exposed carcass tissue in 11 of 18 animals.

The ventral base of the ear injection technique was evaluated in a conditions of use study in 200 beef cattle. Each animal received a single injection of EXCEDE Sterile Suspension at a dose of 6.6 mg CE/kg BW at the base of the ear using the ventral injection technique. Normal restraint was adequate for 95.5% of animals in the study. Injection site scores were normal for 65.3% and 92.5% of cattle on Days 14 and 28, respectively. One animal had an unusually large swelling on Day 7 which reduced to a size comparable to other study animals by Day 14.

Safety Studies in Lactating Dairy Cattle

The local tolerance of the ear to a single subcutaneous injection at the base of the ear of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 114 adult dairy cattle. Successful injection in the base of the ear was achieved in 97.4% of cattle using normal facilities and restraint equipment. No leak back or excessive bleeding was observed following injection for 99.1% of cattle, with injection volumes ranging from 15 to 30 mL. On Days 28 and 56 following injection of EXCEDE Sterile Suspension in the base of the ear, 95.6% and 100% of ears, respectively, were observed as normal with no injection site swelling.

In a residue study, six dairy cows were injected in the base of the ear at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension. No animals exhibited drooping ears at any time after treatment but all animals had signs of swelling at the injection site at all observation times after treatment. Cows were slaughtered 10 days after injection. At necropsy, all six cows showed evidence of injection site inflammation (discoloration of fat tissue/fascia) and four of six cows had discoloration of tissue dorsal and posterior to the ear canal on the carcass. In addition to discoloration, tan nodules and a milky white fluid exudate were also present at the sectioned surface.

Injection site safety for base of the ear administration was evaluated in the metritis effectiveness study described above. Normal restraint was adequate for ≥ 97.8% of injections administered. Injection site scores were normal in 50.3%, 73.2%, and 96.4% at 2 or 3, 11, and 54±3 days after the second injection, respectively.

The ventral and rostral base of the ear injection techniques were compared with the toward the opposite eye technique in a conditions of use study in 197 lactating dairy cattle. Normal restraint was adequate for 89.8% (ventral), 98% (rostral), and 100% (opposite eye) of animals in the study. Injection site scores were normal for 32% (rostral), 46.9% (ventral), and 47.9% (opposite eye) of cattle on Day 14, and 73% (rostral), 87.8% (ventral), and 64.6% (opposite eye) of cattle on Day 28, respectively.

TISSUE AND MILK RESIDUE DEPLETION

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. A separate study established the tolerance for ceftiofur residues in milk. The tolerances for ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support a 13-day pre-slaughter withdrawal period.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur residues in milk were less than tolerances at all time points after treatment. These data collectively support that no milk discard period is required for this product.

Two-Dose Residue Decline Studies

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in the kidney by 13 days after the second dose. These data collectively continue to support a 13-day pre-slaughter withdrawal period after the last dose.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Milk residue decline data from this study supports that no milk discard period is required for this product.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F). Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package sizes:
100 mL vial
250 mL vial

Approved by FDA under NADA # 141-209

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007
www.EXCEDE.com or call 1-888-963-8471

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Naxcel®
brand of ceftiofur sodium
sterile powder

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats.

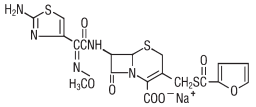
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle, swine, chickens and turkeys for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β -lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur. The pH was adjusted with sodium hydroxide and monobasic potassium phosphate.

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-amino-4-thiazolyl](methoxymino)-acetyl]amino]-3-[[[2-furanyl(carbonyl)thio] methyl]-8-oxo-, monosodium salt, [6R-[6 α ,7 β (Z)]]-

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows:

- 1 gram vial**—Reconstitute with 20 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.
 - 4 gram vial**—Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.
- Shake thoroughly prior to use.

INDICATIONS

Cattle

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melanogenicus*.

Swine

NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis* and *Streptococcus suis*.

Sheep

NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Goats

NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Horses

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.

Dogs

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

Day-Old Chicks

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Day-Old Turkey Poults

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.

DOSAGE AND ADMINISTRATION

Cattle

Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., for respiratory disease, extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite; and for foot rot, extent of swelling, lesion and severity of lameness).

Swine

Administer to swine by intramuscular injection at the dosage of 1.36 to 2.27 mg ceftiofur per pound (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

Sheep

Administer to sheep by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite).

Goats

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at

24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Horses

Administer to horses by intramuscular injection at the dosage of 1.0 to 2.0 mg ceftiofur per pound (2.2 to 4.4 mg/kg) of body weight (2-4 mL reconstituted sterile solution per 100 lbs body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Dogs

Administer to dogs by subcutaneous injection at the dosage of 1.0 mg ceftiofur per pound (2.2 mg/kg) of body weight (0.1 mL reconstituted sterile solution per 5 lbs body weight). Treatment should be repeated at 24-hour intervals for 5-14 days. Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No viral closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Day-Old Chicks

Administer by subcutaneous injection in the neck region of day-old chicks at the dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Day-Old Turkey Poults

Administer by subcutaneous injection in the neck region of day-old turkey poults at the dosage of 0.17 to 0.5 mg ceftiofur/poul. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults. Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) or to report any adverse event please call Zoetis Inc. at 1-888-963-8471.

RESIDUE WARNINGS:

Cattle: When used according to label indications, dosage and routes of administration, treated cattle must not be slaughtered for 4 days following the last treatment. When used according to label indications, dosage and routes of administration, a milk discard time is not required. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Swine: When used according to label indications, dosage and route of administration, treated pigs must not be slaughtered for 4 days following the last treatment. **Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.**

Sheep: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Goats: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Horses: Do not use in horses intended for human consumption.

PRECAUTIONS

The effects of ceftiofur on the reproductive performance, pregnancy, and lactation of cattle, swine, sheep, and goats have not been determined.

Cattle

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Swine

The safety of ceftiofur has not been determined for swine intended for breeding.

Horses

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

Dogs

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2. Testing followed Clinical and Laboratory Standards Institute (CLSI) Guidelines.

Table 1. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC ^{***} (µg/mL)	MIC Range (µg/mL)
Bovine	<i>Mannheimia haemolytica</i>	461	1988-1992	0.06	≤0.03-0.13
	<i>Mannheimia haemolytica</i>	42	1993	0.015	≤0.003-0.03
	<i>Pasteurella multocida</i>	318	1988-1992	0.06	≤0.03-0.25
	<i>Pasteurella multocida</i>	48	1993	≤0.003	≤0.003-0.015
	<i>Histophilus somni</i>	109	1988-1992	0.06	≤0.03-0.13
	<i>Histophilus somni</i>	59	1993	≤0.0019	no range
	<i>Fusobacterium necrophorum</i>	17	1994	≤0.06	no range
Swine	<i>Actinobacillus pleuropn.</i>	83	1993	≤0.03	≤0.03-0.06
	<i>Pasteurella multocida</i>	74	1993	≤0.03	≤0.03-0.06
	<i>Streptococcus suis</i>	94	1993	0.25	≤0.03-1.0
	<i>Salmonella choleraesuis</i>	50	1993	1.0	1.0-2.0
	beta-hemolytic <i>Streptococcus</i> spp.	24	1993	≤0.03	≤0.03-0.06
	<i>Actinobacillus suis</i>	77	1998	0.0078	0.0019-0.0078
	<i>Haemophilus parasuis</i>	76	1998	0.06	0.0039-0.25
Sheep	<i>Actinobacillus haemolytica</i>	39	1992	0.13	≤0.03-0.13
	<i>Pasteurella multocida</i>	23	1992	≤0.03	no range
Canine	<i>Escherichia coli</i>	44	1992	4.0	0.06-64.0
	<i>Escherichia coli</i>	18	1990	0.25	0.13-0.5
	<i>Proteus mirabilis</i>	17	1990	≤0.06	≤0.06-0.5
	<i>Proteus mirabilis</i>	23	1992	1.0	≤0.06-4.0
	<i>Escherichia coli</i>	1204	1995	1.0	0.13->32.0

* Minimum inhibitory concentration (MIC) for 90% of the isolates.

Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Animal	Organism Tested	Number Tested	Date (µg/mL)	MIC ^{***} (µg/mL)	MIC Range
Bovine	<i>Mannheimia haemolytica</i>	110	1997-1998	0.06	≤0.03-0.25
	<i>Mannheimia haemolytica</i>	139	1998-1999	≤0.03	≤0.03-0.5
	<i>Mannheimia haemolytica</i>	209	1999-2000	≤0.03	≤0.03-0.12
	<i>Mannheimia haemolytica</i>	189	2000-2001	≤0.03	≤0.03-0.12
	<i>Pasteurella multocida</i>	107	1997-1998	≤0.03	≤0.03-0.25
	<i>Pasteurella multocida</i>	181	1998-1999	≤0.03	≤0.03-0.5
	<i>Pasteurella multocida</i>	208	1999-2000	≤0.03	≤0.03-0.12
	<i>Pasteurella multocida</i>	259	2000-2001	≤0.03	≤0.03-0.12
	<i>Histophilus somni</i>	48	1997-1998	≤0.03	≤0.03-0.25
	<i>Histophilus somni</i>	87	1998-1999	≤0.03	≤0.03-0.125
	<i>Histophilus somni</i>	77	1999-2000	≤0.03	≤0.03-0.06
	<i>Histophilus somni</i>	129	2000-2001	≤0.03	≤0.03-0.12
	<i>Bacteroides fragilis</i> group	29	1994	16.0	≤0.06->16.0
	<i>Bacteroides</i> spp., non- <i>fragilis</i> group	12	1994	16.0	0.13->16.0
	<i>Peptostreptococcus anaerobius</i>	12	1994	2.0	0.13-2.0
	<i>Actinobacillus pleuropn.</i>	97	1997-1998	≤0.03	no range
	<i>Actinobacillus pleuropn.</i>	111	1998-1999	≤0.03	≤0.03-0.25
Swine	<i>Actinobacillus pleuropn.</i>	126	1999-2000	≤0.03	≤0.03-0.06
	<i>Actinobacillus pleuropn.</i>	89	2000-2001	≤0.03	≤0.03-0.06
	<i>Pasteurella multocida</i>	114	1997-1998	≤0.03	≤0.03-1.0
	<i>Pasteurella multocida</i>	147	1998-1999	≤0.03	≤0.03-0.5
	<i>Pasteurella multocida</i>	173	1999-2000	≤0.03	≤0.03-0.06
	<i>Pasteurella multocida</i>	186	2000-2001	≤0.03	≤0.03-0.12
	<i>Streptococcus suis</i>	106	1997-1998	0.5	≤0.03-4.0
	<i>Streptococcus suis</i>	142	1998-1999	0.25	≤0.03-1.0
	<i>Streptococcus suis</i>	146	1999-2000	0.06	≤0.03-4.0
	<i>Streptococcus suis</i>	167	2000-2001	0.06	≤0.03-4.0
	<i>Salmonella choleraesuis</i>	96	1999-2000	1.0	0.03->4.0
	<i>Salmonella choleraesuis</i>	101	2000-2001	1.0	0.5-2.0
Equine	<i>Streptococcus equi</i> subsp. <i>equi</i>	12	1994	≤0.0019	no range
	<i>Streptococcus equi</i> subsp. <i>equi</i>	29	2002	≤0.03	≤0.03-0.05
	<i>Streptococcus zooepidemicus</i>	48	1994	≤0.0019	no range
	<i>Streptococcus zooepidemicus</i>	59	2002	≤0.03	≤0.03-0.25
	<i>Rhodococcus equi</i>	66	1998	4.0	≤0.03-16.0
	<i>Rhodococcus equi</i>	42	2002	8.0	≤0.03->32.0
	<i>Bacteroides fragilis</i> group	32	1995	>16.0	0.13->16.0
	<i>Bacteroides</i> spp., non- <i>fragilis</i> group	12	1995	4.0	0.25-4.0
	<i>Fusobacterium necrophorum</i>	16	1995	≤0.06	no range
	<i>Escherichia coli</i>	26	2000	32	0.25->32
Canine	<i>Proteus mirabilis</i>	14	2000	0.25	0.06-0.25
	<i>Escherichia coli</i>	17	1998-1999	1.0	0.25-1.0
	<i>Escherichia coli</i>	25	1999-2000	0.50	0.12-0.5
	<i>Escherichia coli</i>	20	2000-2001	2.0	0.12-16.0
	<i>Citrobacter</i> spp.	37	1995	32.0	0.5->32.0
	<i>Enterobacter</i> spp.	51	1995	>32.0	0.13->32.0
	<i>Klebsiella</i> spp.	100	1995	1.0	0.13-2.0
	<i>Proteus</i> spp.	19	1995	1.0	0.06-32.0
	<i>Pseudomonas</i> spp.***	31	1995	>32.0	0.06->32.0
	<i>Salmonella</i> spp.	24	1995	1.0	0.5-1.0
	<i>Staphylococcus</i> spp. (coagulase positive)	17	1995	2.0	1.0-2.0
	<i>Staphylococcus</i> spp. (coagulase negative)	26	1995	8.0	0.13->32.0
Chicken	<i>Escherichia coli</i>	62	1997-1998	0.50	0.25-2.0
	<i>Escherichia coli</i>	53	1998-1999	4.0	0.25->4.0
	<i>Escherichia coli</i>	67	1999-2000	0.50	0.12-16.0
	<i>Escherichia coli</i>	90	2000-2001	1.0	≤0.03-8.0

* The following *in vitro* data are available but their clinical significance is unknown.

** Minimum inhibitory concentration (MIC) for 90% of the isolates.

*** MIC₉₀ is 32 µg/mL

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are 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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by CLSI.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

Standardized procedures¹ require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

Table 3. Acceptable quality control ranges for ceftiofur against Clinical and Laboratory Standards Institute recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter* (mm)	MIC Range (µg/mL)
<i>Escherichia coli</i> (25922)	26–31	0.25–1.0
<i>Staphylococcus aureus</i> (29213)	—	0.25–1.0
<i>Staphylococcus aureus</i> (25923)	27–31	—
<i>Pseudomonas aeruginosa</i> (27853)	14–18	16.0–64.0
<i>Actinobacillus pleuropneumoniae</i> (27090)	34–42**	0.004–0.015***
<i>Histophilus somni</i> (700025)	36–46**	0.0005–0.004***

* All testing performed using a 30µg disk.
** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% CO₂ for 20-24 hours.
*** MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM).

ANIMAL SAFETY

Cattle

Results from a five-day tolerance study in normal feeder calves indicated that formulated ceftiofur was well tolerated at 25 times (25 mg/lb/day) the highest recommended dose of 1.0 mg/lb/day for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were intramuscularly administered formulated ceftiofur at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg/lb/day to determine the safety factor. There were no adverse systemic effects indicating that the formulated ceftiofur has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg/lb/day) the recommended dose for three times (15 days) the recommended three to five days of therapy. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at 1 and 3 times the highest recommended dose of 1.0 mg/lb/day. The histopathological evaluations were conducted at posttreatment days 1, 3, 7 and 14.

The injection of NAXCEL Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated. However, a several square centimeter area of yellow-red discoloration resulting from a single SC injection persisted in many of the cattle beyond 4.5 days post-injection. Also, one of the animals developed an abscess at the injection site.

Swine

Results from a five-day tolerance study in normal feeder pigs indicated that formulated ceftiofur was well tolerated when administered at 57 mg/lb (more than 25 times the highest recommended daily dosage of 2.27 mg/lb of body weight) for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety factor and to measure the muscle irritancy potential in swine, a safety/toxicity study was conducted. Five barrows and five gilts per group were intramuscularly administered formulated ceftiofur at 0, 2.27, 6.81 and 11.36 mg/lb of body weight for 15 days which is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb of body weight/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects indicating that formulated ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg/lb/day for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at posttreatment days 1, 2, 3 and 4. By day 10 post injection the muscle reaction was subsiding and at day 15 post injection there was little evidence of muscle damage in any of the pigs in any of the treatment groups.

Sheep

In a 15-day safety/toxicity study in sheep, three wether and three ewe lambs per group were given formulated ceftiofur sodium by the intramuscular route 0 (sterile water vehicle), 1, 3 or 5 times the recommended dose of 1.0 mg/lb/day for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in sheep. Based on examination of injection sites from study days 9, 11, 13 and 15, a low incidence of visual changes and histopathologic findings of mild, reversible inflammation from all groups including the controls indicated that the formulation is a slight muscle irritant.

Goats

In a 15-day safety/toxicity study 5 lactating does, 5 dry does, and 5 wethers were given formulated ceftiofur by the intramuscular route with 11 mg/kg/day for 15 days. This constitutes 5 times the recommended dose for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in goats.

Horses

In a safety study, horses received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1.0 mg/lb/day (50 mg/mL), 3.0 mg/lb/day (100 mg/mL), or 5.0 mg/lb/day (200 mg/mL) of an aqueous solution of ceftiofur sodium for 30 or 31 days. Ceftiofur sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/lb/day for 30 or 31 days. No clinical evidence of irritation was noted at any dose. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3.0 or 5.0 mg/lb/day ceftiofur, and general mild skeletal muscle irritation at the injection sites which resolved by regeneration of muscle fibers.

In a tolerance study, horses received a single daily intravenous infusion of either 0 (saline), 10.0 or 25.0 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for 10 days. The results indicated that ceftiofur administered intravenously at a dose of 10.0 or 25.0 mg/lb/day apparently can change the bacterial flora of the large intestine thereby leading to inflammation of the large intestine with subsequent diarrhea and other clinical signs (loose feces, eating bedding straw, dehydration, rolling or colic and a dull, inactive demeanor). Decreased food consumption, a loss of body weight, hematologic changes related to acute inflammation and stress, and serum chemistry changes related to decreased food consumption and diarrhea were also associated with treatment at these doses. The adverse effects were most severe a few days after dosing was initiated and tended to become less severe toward the end of the 10-day dosing period.

Dogs

Ceftiofur sodium was well tolerated at the therapeutic dose and is safe for the treatment of urinary tract infections in dogs. In the acute safety study, ceftiofur was well tolerated by dogs at the recommended level (1.0 mg/lb) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four females developed thrombocytopenia (15 days) and anemia (36 days). Thrombocytopenia and anemia also occurred at the 3X and 5X dose levels. In the reversibility phase of the study (5X dose), the thrombocytopenia reversed within 8 days, and of the two anemic animals the male recovered within 6 weeks and the female was sacrificed due to the severity of the anemia.

In the 15-day tolerance study in dogs, high subcutaneous doses (25 and 125 times the recommended therapeutic dose) produced a progressive and dose-related thrombocytopenia, with some dogs also exhibiting anemia and bone marrow changes. The hematopoietic changes noted in dogs treated with ceftiofur were similar to those associated with long-term cephalosporin administration in dogs and also man. The hematopoietic effects are not expected to occur as a result of recommended therapy.

Day-Old Chicks

In an acute toxicity study of ceftiofur in day-old chicks, a total of 60 male and 60 female chicks were each given single subcutaneous injections of 10, 100 or 1,000 mg/kg of body weight. Treatment on day 1 was followed by 6 days of observation; body weight was determined on days 1, 4 and 7; and selected hematology parameters were evaluated on day 4. No meaningful differences were noted among the treated and control groups of chicks for the parameters evaluated. Histopathologic evaluation of all deaths and chicks surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 20 times (100 mg/kg) the intended highest use dosage.

Day-Old Turkey Poults

In an acute toxicity study of ceftiofur in day-old turkey poults, a total of 30 male and 30 female poults were each administered single subcutaneous injections of 100, 400 or 800 mg/kg body weight. Injection on day 1 was followed by 6 days of observation; body weight on days 1, 4, and 7; and selected hematology parameters on day 4. No meaningful differences were noted between the treated groups at 100 or 400 mg ceftiofur/kg and a negative control group for the parameters evaluated. Histopathologic evaluation of all deaths and poults surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 50 times (400 mg/kg) the highest use dosage. A dose of 800 mg/kg (100 times the intended highest use dosage) was toxic, resulting in clinical signs and deaths accompanied by gross and microscopic morphologic tissue alterations.

TISSUE RESIDUE DEPLETION

Cattle

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. These tolerances of ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle, and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in cattle. In this study, cattle received an intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in cattle when used according to label directions.

Swine

Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver, and muscle. These tolerances of ceftiofur residues are 0.25 ppm in kidney, 3.0 ppm in liver and 2.0 ppm in muscle.

A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

STORAGE CONDITIONS

Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F).

Store **reconstituted** product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) for up to 12 hours.

Protect from light. Color of the cake may vary from off-white to a tan color. Color does not affect potency.

ONE-TIME SALVAGE PROCEDURE FOR RECONSTITUTED PRODUCT

At the end of the 7-day refrigeration or 12-hour room temperature storage period following reconstitution, any remaining reconstituted product may be frozen for up to 8 weeks without loss in potency or other chemical properties. This is a one-time only salvage procedure for the remaining product. To use this salvaged product at any time during the 8-week storage period, hold the vial under warm running water, gently swirling the container to accelerate thawing, or allow the frozen material to thaw at room temperature. Rapid freezing or thawing may result in vial breakage. Any product not used immediately upon thawing should be discarded.

HOW SUPPLIED

NAXCEL Sterile Powder is available in the following package sizes:

**1 gram vial
4 gram vial**

¹ Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

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The Zoetis logo, consisting of the word "zoetis" in a lowercase, orange, sans-serif font.