Naxcel®

brand of cefitofur 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 chicks and day-old turkey pouls.

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 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.

**DOSE AND ADMINISTRATION**

NAXCEL Sterile Powder contains the sodium salt of cefitofur which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacterial pathogens.** In cattle, including Haemophilus influenzae, Haemophilus somnus, Pasteurella multocida, and Klebsiella pneumoniae, cefitofur is bactericidal in vitro, resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains cefitofur sodium equivalent to 50 mg cefitofur. The pH was adjusted with sodium hydroxide and mono-basic potassium phosphate.

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Chemical Structure of Cefitofur Sodium

![Chemical Structure of Cefitofur Sodium](image)

**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 cefitofur sodium equivalent to 50 mg cefitofur.

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

**INDICATIONS**

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, abscesses) associated with Fusobacterium necrophorum and Bacteroides melaninogenicus.

NAXCEL Sterile Powder is indicated for treatment of swine, poultry and turkeys for the treatment of disease associated with E. coli, Salmonella spp., and Staphylococcus aureus.

In sheep, NAXCEL Sterile Powder is indicated for treatment of respiratory disease (sheep pneumonia) associated with Mycoplasma mycoides and Pasteurella multocida.

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

**GOATS**

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

**DOGS**

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

Day-Old Chicks

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

Day-Old Turkey Pouls

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

**DOSAGE AND ADMINISTRATION**

**CATTLE**

Cattle—Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0.5 to 1.0 mg/cow per pound (2.2 to 4.4 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hr 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 and character of respiratory sounds and/ or mucous exudate). Pharmacokinetic data indicate that elimination of the drug is more rapid in doing 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 cefitofur per pound (2.2 to 4.4 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 and character of respiratory sounds and/ or mucous exudate). Pharmacokinetic data indicate that elimination of the drug is more rapid in doing does, the high end of the dose range is recommended.

**SWINE**

Administer to swine by intramuscular injection at the dosage of 0.5 to 1.0 mg/cow per pound (2.2 to 4.4 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 and character of respiratory sounds and/ or mucous exudate). Pharmacokinetic data indicate that elimination of the drug is more rapid in doing does, the high end of the dose range is recommended.

**SHEEP**

Administer to sheep by intramuscular injection at the dosage of 0.5 to 1.0 mg/cow per pound (2.2 to 4.4 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 and character of respiratory sounds and/ or mucous exudate). Pharmacokinetic data indicate that elimination of the drug is more rapid in doing does, the high end of the dose range is recommended.

**GOATS**

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg/cow per pound (2.2 to 4.4 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 and character of respiratory sounds and/ or mucous exudate). Pharmacokinetic data indicate that elimination of the drug is more rapid in doing does, the high end of the dose range is recommended.

**Dogs**

Administer to dogs by subcutaneous injection at the dosage of 0.5 mg cefitofur 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 given by subcutaneous injection. No vial closure should be entered more than 20 times. Treatment at less than 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 0.006-0.02 mg/meal (0.1 to 0.5 mg/mL). The reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

**Day-Old Turkey Pouls**

Administer by subcutaneous injection in the neck region of day-old turkey pouls at the dosage of 0.17 to 0.5 mg cefitofur/poult. One mL of the 50 mg reconstituted solution will treat approximately 250 to 625 day-old pouls.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

**Poultry**

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

**Residue Warnings**

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

**WARNINGS**

FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitive individuals, including, but not limited to, rash, urticaria, bronchospasm, anaphylaxis, and death. Deaths have been reported in humans with a history of penicillin or cephalosporins allergy. 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 respiratory irritation occurs (e.g., skin, rash, headache, difficult breathing), seek medical attention.

The material safety data sheet contains important 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.

**PRECAUTIONS**

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

**ADVERSE REACTIONS**

The use of cefitofur may result in some signs of immediate and transient local pain at injection sites.

**CLINICAL MICROBIOLOGY**

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

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*Minimum inhibitory concentration (MIC) for 90% of the isolates.*
Based on the pharmacokinetic studies of cephalothin in swine and cattle after a single intramuscular injection of 1 mg cephalothin equivalent/lb (2.2 mg/kg BW), clinical effectiveness data and MIC data, the following breakpoint is recommended by 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 CSL.

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>≤ 2.0</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>18–20</td>
<td>4.0</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>6–17</td>
<td>&gt; 8.0</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

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 test result may be used to guide therapy. It is a safer approach to use the recommended dose in a patient where drug is physiologically concentrated. A report of “Resistant” indicates that the achievable blood drug concentrations are unlikely to be inhibitory and other therapy should be selected.

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>≤ 0.25</td>
<td>(S) Susceptible</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Organism Name (ATCC Number)</th>
<th>Zone Diameter (mm)</th>
<th>MIC Range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli (25922)</td>
<td>26–31</td>
<td>0.25–1.0</td>
</tr>
<tr>
<td>Staphylococcus aureus (29213)</td>
<td>—</td>
<td>0.25–1.0</td>
</tr>
<tr>
<td>Staphylococcus aureus (29232)</td>
<td>27–31</td>
<td>—</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (27675)</td>
<td>14–18</td>
<td>0.004–0.004***</td>
</tr>
<tr>
<td>Actinobacillus pleomorphus (9678)</td>
<td>34–42**</td>
<td>0.004–0.015**</td>
</tr>
<tr>
<td>Helicobacter ssp (700025)</td>
<td>36–48**</td>
<td>0.005–0.004***</td>
</tr>
</tbody>
</table>

* 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% CO2, for 24–28 hours. *** MIC quality 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 cephalothin was well tolerated at 25 times (25 mg/kg/day) the highest recommended dose of 1.0 mg/kg/day for five consecutive days. Cephalothin 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 1.36 to 2.27 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by CSL.

<table>
<thead>
<tr>
<th>TISSUE RESIDUE DEPLETION</th>
</tr>
</thead>
</table>

Sheep

In a 15-day safety/toxicity study in sheep, three wether and three ewe lambs per group were given formulated cephalothin sodium by the intramuscular route at 0, 2.5, 5.0, 7.5 or 10.0 mg/kg body weight (2.2 mg/kg/day) for 10 days. There were no adverse systemic effects indicating that formulated cephalothin 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 associated with injected site inflammation was noted in 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 cephalothin by the intramuscular route with no adverse systemic effects noted 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 cephalothin 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 0.6 mg/kg/day (saline control), 1.0 mg/kg/day (50 mg/mL), 3.0 mg/kg/day (100 mg/mL), or 0.6 mg/kg/day (0.1 mg/mL) of an aqueous suspension of cephalothin sodium for 30 or 31 days. Cephalothin sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/kg for 30 or 31 days. No clinical evidence of infection 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 mg/kg/day, 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 0.6 mg/kg/day (saline control), 10.0 mg/kg/day and 25.0 mg/kg/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, inappetent demeanor). Decreased food consumption, changes in 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

Cephalothin 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, cephalothin was well tolerated by dogs at the recommended level (1.0 mg/kg) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four female developed thrombocytopenia (15 days) and anemia (26 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 (125 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 cephalothin were similar to those associated with long-term cephalaxin 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 cephalothin in day-old chicks, a total of 60 male and 60 female chicks were given single subcutaneous injections of 10, 100, and 1,000 mg/kg body weight on day 1, followed by additional treatments on days 2, 4, and 7. The hematopoeitic effects are not expected to occur as a result of recommended therapy.

Day-Old Turkeys

In an acute toxicity study of cephalothin in day-old turkey pouls, a total of 30 male and 30 female pouls 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 was determined on days 1, 4, and 7; and selected hematopoeitic parameters were evaluated on day 4. No meaningful differences were noted between the treated group of chicks and a control group evaluated. Histopathologic evaluation of all internal deaths and pouls surviving to termination did not reveal a target organ or tissue of potential toxicity in cephalothin administered at up to 50 times (1000 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 cephalothin residues in cattle, liver, kidney, and muscle. These tolerances for residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle, and 0.1 ppm in milk.

A pilot tissue residue study conducted in cattle in this study, cattle received an intramuscular injection of 1.0 mg of cephalothin per lb body weight (2.2 mg of cephalothin per kg body weight) for five consecutive days. There were no adverse systemic effects indicating that formulated cephalothin is well tolerated and has a wide margin of safety in cattle 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

A radiolabeled residue metabolism study established tolerances for cephalothin residues in swine, kidney, liver, and muscle. These tolerances of cephalothin residues are 0.25 ppm in kidney, 3.0 ppm in liver and 2.0 ppm in muscle.

A pilot tissue residue study conducted in swine. In this study, pigs received 2.27 mg of cephalothin per lb body weight (5 mg of cephalothin per kg body weight) for three consecutive days. Cephalothin residues in tissues were less than the tolerances for cephalothin 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.