Approval Date: July 13, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-338

B. Sponsor

The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

C. Proprietary Name

NAXCEL® Sterile Powder

D. Established Name

ceftiofur sodium

E. Dispensing Status

OTC, Rx, or VFD

F. Dosage Regimen

NAXCEL Sterile Powder should be reconstituted as follows:

1 gram vial - Reconstitute with 20 mL Sterile Water for Injection or Bacteriostatic 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 or Bacteriostatic Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Store unreconstituted product in a refrigerator 2 ° -8 ° C (36 ° -46 ° F). Store reconstituted product either in a refrigerator 2 ° -8 ° C (36 ° -46 ° F) for up to seven days or at controlled room temperature 15 ° -30 ° C (59 ° -86 ° F) for up to 12 hours. Reconstituted NAXCEL can be frozen for up to eight weeks without loss in potency or other chemical properties. Carefully thaw the frozen material under warm to hot running water, gently swirling the container to accelerate thawing. The frozen material may also be thawed at room temperature.

Administer by intramuscular injection to horses at a dosage of 1.0-2.0 mg per pound of body weight (2.2-4.4 mg/kg). Treatment should be repeated every 24 hours. At the concentration of 50 mg/mL, this dose requires a treatment volume of 2-4 mL reconstituted sterile solution per 100 lb 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

G. Indication

Exactly from label NAXCEL Sterile Powder is indicated for the treatment of respiratory infections in horses associated with Streptococcus zooepidemicus.

H. Effect of Supplement

The supplement provides data in support of a request for approval of Naxcel ® Sterile Powder for an additional species (equine). The issue of the Freedom of Information (FOI) Summary should be considered an extension of previously approved version describing data in support of Naxcelreg., NADA 140-338, approved as a treatment for respiratory disease in cattle January 25, 1988.

II. EFFECTIVENESS

A. Pivotal Studies

1. Determination of Dose

a. Introduction

The [[beta]]-lactam class of antibiotics work primarily on infections located in the extracellular spaces of the body. For these types of antibiotics, plasma drug concentrations are more closely related to efficacy than are tissue homogenate concentrations. In tissue homogenates, the active drug concentration at the infection site is diluted by the intracellular fluid volumes released during the homogenization process. Thus, historically from literature, the [[beta]]-lactam pharmacokinetic value most correlated with efficacy is the time above the minimum inhibitory concentration, not maximum plasma concentration (Cmax) or area under the curve (AUC). Accordingly, the antimicrobial activity of ceftiofur and its active desfuroylceftiofur metabolites depends on the extracellular tissue concentrations. Substantial historical information with the use of ceftiofur sodium in three species for which it is approved (i.e., bovine, poultry, swine) indicates that, at efficacious doses, plasma concentrations of ceftiofur and desfuroylceftiofur metabolites remain above the minimum inhibitory concentration (MIC) of the target pathogens for the interval between injections. The well established relationship of dose/blood concentration/efficacy in the bovine was bridged to the blood concentration/time profile in the horse. In the bovine at the approved dosage regimen (0.5-1.0 mg ceftiofur equivalents/lb body weight administered intramuscularly once daily for 3-5 days), concentrations remain at or above 0.2 µg ceftiofur equivalents/mL plasma for the entire interval between doses. This is several-fold higher than the MIC required to inhibit 90% of the tested isolates associated with bovine respiratory disease (MIC(90)) < = 0.06 µg ceftiofur equivalents/mL). Based on the above data, an efficacious dose of ceftiofur sodium in horses was predicted. The efficacious dose is defined as one which results in blood concentrations of ceftiofur and its desfuroylceftiofur metabolites exceeding the MIC(90) of the target pathogen (Streptococcus zooepidemicus) throughout the dosing interval. Since the dose extrapolation depends on the assumption that the penetration of ceftiofur and its active metabolites into the equine and bovine pulmonary tissues are comparable, the bovine and equine ratio of blood/lung homogenate concentrations were compared. Thus, an appropriate equine ceftiofur dose was derived on the basis of: 1) plasma pharmacokinetics, particularly, the time above MIC(90) versus either Cmax or AUC, and 2) verification that ceftiofur plasma pharmacokinetics can predict drug concentrations within the equine lung.

b. **Miminimum Inhibitory Concentration (MIC) Studies**

Minimum Inhibitory Concentration Determinations of Ceftiofur for Bacterial Isolates Collected From A Clinical Efficacy Study (Ceftiofur vs. Placebo)

Investigators
Drs. R.J. Yancey, C.A. Case, R.A. Rzepkowski, S.D. Folz
The Upjohn Company
Kalamazoo, MI

This in vitro study used bacterial isolates collected from the respiratory tract of treated and control horses (60) with respiratory infections from the Confirmation of Dose Study: Ceftiofur vs. Placebo (See IV. A. 2. b.). MICs of 101 clinically isolated pathogens, representing 12 genera and 20 species, were determined for ceftiofur sodium and twelve comparator antimicrobial compounds or combinations (amikacin, amoxicillin, ampicillin, cephalothin, chloramphenicol, ciprofloxacin, erythromycin, gentamicin, penicillin G, sulfamethoxazole, tetracycline, and trimethoprim/ sulfadiazine). Of the 101 isolates, 51 were identified as Streptococcus zooepidemicus . The isolates were obtained by transtracheal wash and/or nasopharyngeal swab. The Streptococcus zooepidemicus isolates were very sensitive to ceftiofur and the other [[beta]]-lactam antibiotics. The MIC(90) for all the [[beta]]-lactam antibiotics was determined to be < = 0.06 µg/mL, except for amoxicillin. Streptococcus zooepidemicus was less sensitive to the other compounds tested, except for erythromycin which also had an MIC(90) of < = 0.06 µg/mL. In general, ceftiofur was the most active compound against all the bacterial isolates tested, except for Bordetella bronchiseptica and Pseudomonas spp. The resistance of these gram-negative, nonfermentors from horses is similar to the MIC values previously reported for these bacteria from other animals.

Minimum Inhibitory Concentration Determinations of Ceftiofur for Bacterial Isolates Collected From A Clinical Efficacy Study (Ceftiofur vs. Ampicillin)

Investigators
Dr. R. D. Walker
Michigan State University
East Lansing, MI

Dr. S. D. Folz
The Upjohn Company
Kalamazoo, MI

This in vitro study used bacterial isolates from the respiratory tract of horses with respiratory infections from the Confirmation of Dose Study: Ceftiofur vs. Ampicillin (17 horses, See IV. A. 2. c.) and the corroborative Equine Clinical Study: Ceftiofur vs. Ampicillin, (29 horses, See IV. B. 1.) The isolates were collected by transtracheal wash and/or nasopharyngeal swabs. MICs of 62 clinically isolated pathogens were determined for ceftiofur sodium and seven comparator antimicrobial compounds (ampicillin sodium, erythromycin, gentamicin, penicillin G, tetracycline hydrochloride, sulfadiazine and trimethoprim). Of the 62 isolates, 38 (61%) were identified as Streptococcus zooepidemicus (10 isolates from the 17 horse study and 28 from the 29 horse study). They were obtained from horses from the following geographically diverse states: CO, IL, KY, MI, OH, TN and VA. Beta-hemolytic streptococci, Pasteurella spp. and Escherichia coli were previously reported as aerobic

bacteria most frequently associated with equine respiratory disease. In this study, 40 (64%) of the isolates were beta-hemolytic streptococci (Streptococcus zooepidemicus was represented by 38 (95%) of the beta-hemolytic streptococci) and 6 (10%) were Pasteurella spp. The remaining isolates were a variety of bacterial species. The ceftiofur MICs for all the beta-hemolytic streptococci were < = 0.03 µg/mL and a mean 0.27 µg/mL for the Pasteurella spp. The other comparator drugs exhibited less in vitro activity against the same equine isolates.

Minimum Inhibitory Concentrations for Ceftiofur and Desfuroylceftiofur With Isolates of Veterinary Importance

Investigators
Sarah A. Salmon, Jeffrey L. Watts, Robert J. Yancey, Jr.,
Cheryl A. Case
The Upjohn Company
Kalamazoo, MI

The purpose of this study was to compare the in vitro activity of ceftiofur and desfuroylceftiofur (main metabolite of the parent compound) against bacterial pathogens of veterinary significance from equine and other domestic species. They were evaluated for in vitro activity against Escherichia coli (n = 40), Haemophilus somnus (n = 59), Actinobacillus pleuropneumoniae (n = 50), Streptococcus equi (n = 12), and Streptococcus zooepidemicus (n = 48); the later two pathogens were isolated from horses with respiratory infections. Within the limitations of the assay, ceftiofur and desfuroylceftiofur were identical in activity against the gram-negative organisms. The MIC(90) for both ceftiofur and desfuroylceftiofur against E. coli was 0.5 µg/mL; 0.0078 µg/mL and 0.015 µg/mL , respectively, for A. pleuropneumoniae ; < = 0.0019 µg/mL for H. somnus, and < = 0.0019 µg/mL and 0.03 µg/mL, respectively, for streptococci. Although desfuroylceftiofur was less active in vitro than ceftiofur against the streptococcal species tested, both compounds are highly active.

c. **Equine Pharmacokinetic Study**

Investigators
P.S. Jaglan, T.S. Arnold, R.D. Roof, T.D. Cox, D.R. Reeves, T.F. Flook
The Upjohn Company
Kalamazoo, MI

The primary objective of this study was to determine a dose which would produce a blood concentration above the MIC(90) of the target equine respiratory pathogen (Streptococcus zooepidemicus). Four Quarter Horse male horses and eight mixed-breed female horses, weighing 972 to 1360 lb, were injected intramuscularly with a single bolus dose of 1 mg ceftiofur equivalents/lb body weight (2.2 mg ceftiofur equivalents/kg body weight). Groups of four horses each were euthanized at 1, 12, and 24 hours after treatment, and total lung tissues were collected. Blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours postdosing or up until the time of euthanasia. For each experimental subject, the plasma and lung concentrations of ceftiofur and all desfuroylceftiofur metabolites were determined by their conversion to desfuroylceftiofur acetamide and the subsequent measurement of desfuroylceftiofur acetamide by HPLC and UV detection.

The average maximum plasma concentration of ceftiofur and desfuroylceftiofur metabolites (Cmax) of 4.46 +/- 0.93 µg ceftiofur equivalents/mL of plasma occurred 1.25 ± 0.46 hours after injection. These concentrations declined to 0.99 ± 0.16, 0.47 ± 0.15, and 0.17 ± 0.02 µg ceftiofur equivalents/mL of plasma at 8, 12, and 24 hours, respectively, after injection. Plasma concentrations were above the minimum concentration required to inhibit 90% of the isolates tested (MIC(90)) for the entire 24-hour period (i.e. the interval between doses). These results are similar to those obtained in the bovine at the lower end of the approved bovine dosage range of 0.5-1.0 mg/lb. The mean residence time of ceftiofur and desfuroylceftiofur metabolites was estimated to be 4.6 ± 1.0 hours.

To verify that the equine plasma level data adequately reflect the drug concentrations in the target organ, the bovine ratio and equine ratio of blood/lung homogenate drug concentrations (ceftiofur and desfuroylceftiofur metabolites) were compared. This ratio provides valuable insight into the similarity of drug penetration into the target organ of both animal species. Because of errors associated with the relationship of total lung homogenate drug concentrations to the MIC values for the target respiratory pathogen (see IV. A. 1. a., Introduction), it was necessary to use the ratio of blood/tissue drug concentrations in lieu of using lung homogenate concentrations alone.

The measured total lung homogenate concentrations of ceftiofur and its desfuroylceftiofur metabolites in horses were 1.40 ± 0.36, 0.27 ± 0.07, and 0.15 ± 0.08 µg ceftiofur equivalents/g of lung tissue (wet weight) at 1, 12, and 24 hours after dosing, respectively. The equine lung homogenate concentrations at 12 and 24 hours after injection were similar to those plasma concentrations observed at the corresponding blood sampling times. In general, the ratio of plasma/lung homogenate concentration observed in the equine study was equal to or greater than those estimated from the bovine study, thus supporting the contention that the penetration of ceftiofur and its desfuroylceftiofur metabolites into the pulmonary extravascular spaces of the equine is equal to or greater than that observed in the bovine.

d. **Conclusions Regarding Determination of Dose**
Intramuscular administration of 1.0 mg ceftiofur equivalents/lb of body weight to horses resulted in rapid absorption; Cmax was achieved within 1-2 hours after injection. Concentrations of ceftiofur and desfuroylceftiofur metabolites in the plasma remained above the MIC(90) for the targeted respiratory pathogen (Streptococcus zooepidemicus , MIC(90) <= 0.06 µg ceftiofur equivalents/mL) for 24 hours after treatment, the projected dosing interval. Comparison of the lung homogenate data from the equine and the bovine indicate that ceftiofur and desfuroylceftiofur metabolites readily diffuse from the plasma into the pulmonary extracellular spaces. These data indicate that the target tissue (lung) is exposed to concentrations of ceftiofur and desfuroylceftiofur metabolites that exceed the MIC(90) of the respiratory pathogens of interest for the majority of the dosing interval. It is on that basis that the dose of 1.0 mg ceftiofur equivalents/lb of body weight was deemed appropriate for confirming drug efficacy in clinical/field trials.

2. **Confirmation of Dose**

a. Introduction

The combination of pharmacokinetic and in vitro data was utilized in determining the potentially effective dose of 1 mg/lb given SID (once a day) intramuscularly. This dose was then taken to the field and evaluated for safety and efficacy under actual conditions of use in two well-controlled clinical studies. In one clinical study, ceftiofur and a placebo were used, and the second study utilized ceftiofur and ampicillin. The 2 mg/lb ceftiofur dose, the upper dose of the recommended dosage range, was established on the basis of safety data generated in the target animal safety study. The safety data are presented in the Safety section of this document.

b. Equine Clinical Study (Ceftiofur vs. Placebo)

Investigator
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College of Veterinary Medicine
Urbana, IL

This was a blinded, well-controlled clinical efficacy study. Sixty (60) horses with naturally acquired respiratory infections were randomly assigned to two study groups: 30 to ceftiofur and 30 to the placebo (saline) group. A transtracheal wash (TTW) and a nasopharyngeal swab (NPS) were performed on each horse. From the TTWs, Streptococcus zooepidemicus was cultured from 26 of the 30 ceftiofur treated horses and from 25 of the 30 placebo treated, a total of 51 isolates. The results obtained via the NPS were similar to those obtained by the TTW procedure: ceftiofur, 28/30; and 25/30 of the placebo cultured positive for Streptococcus zooepidemicus. Streptococcus is considered an opportunistic pathogen infrequently isolated form a transtracheal wash taken from normal horses (1 Sweeney CR, Beech J, Roby KA. Bacterial isolates from tracheobronchial aspirates of healthy horses. Am J Vet Res, Vol 46, No 12, 1985.) . Other pathogens isolated include Actinobacillus spp., Aeromonas spp., Bordetella spp., Corynebacterium spp., Klebsiella spp., Moraxella spp., Pasteurella spp., Pseudomonas spp., Staphylococcus spp., and Streptococcus spp.

Ceftiofur was administered at 1 mg/lb (2.2 mg/kg) SID intramuscularly, and saline was administered at the same volume and in the same manner as ceftiofur. Both treatments were continued for 48 hours after the animals became afebrile and asymptomatic, but did not exceed 10 days of therapy. The mean treatment duration for the ceftiofur treated group was 8.2 ± 0.4 days and for the controls 9.9 ± 0.1 days.

Twenty-eight (93%) of the horses treated with ceftiofur showed clinical improvement and 2 (7%) were classified as failures on the last day of treatment; whereas, only 6 (20%) of the controls improved and 24 (80%) were failures. Clinical improvement is defined as near disappearance of all clinical signs or fully recovered on the last day of treatment. Body temperature reduction on the third day after two treatments (days 1 & 2) was significantly greater ($P<0.01$) for the ceftiofur group than for the controls (1.49 vs. 0.03 ° F, respectively).

Day 7 post-treatment evaluation for the 28 horses treated with ceftiofur that showed clinical improvement on the last day of treatment revealed that 26 horses completely recovered/cured, 1 remained the same, and 1 relapsed. Of the two ceftiofur horses that were treatment failures on the last day of

treatment, one remained a failure and one partially recovered on the Day 7 post-treatment evaluation.

Day 7 post-treatment evaluation for the 6 control horses that showed clinical improvement on the last day of treatment revealed that one fully recovered and the remaining 5 relapsed. Of the 24 control horses that were treatment failures on the last day of treatment, 11 were failures, 9 partially improved and 4 recovered on the Day 7 post-treatment evaluation.

Ceftiofur was well tolerated by the animals treated. There were no adverse reactions in either treatment group.

c. Equine Clinical Study (Ceftiofur vs. Ampicillin)

Investigators
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This was a blinded, well-controlled clinical efficacy study in horses with naturally acquired respiratory infections. This study was designed to compare the therapeutic efficacy of ceftiofur sodium (1.0 mg/lb, 2.2 mg/kg; SID) with ampicillin sodium, FDA approved, as the positive control drug at its recommended treatment level of 3 mg/lb (6.6 mg/kg, given BID [two treatments per day]). Both treatments were continued for 48 hours after clinical symptoms were no longer evident (maximum of 10 days).

Seventeen (17) horses with naturally acquired respiratory infections were included in the study: nine were treated with ceftiofur and eight with ampicillin. On the basis of pretreatment characteristics, the two treatment groups were comparable. Clinical improvement (last day of treatment) was recorded for 9 (100%) of the patients treated with ceftiofur and 7 (88%) of the animals receiving ampicillin. Complete recovery/cure (assessment on the last day of treatment) was noted for 8 (89%) of the ceftiofur patients and 6 (75%) of those treated with ampicillin.

At Day 7 post-treatment, 9 (100%) of the ceftiofur patients and 5 (63%) of the horses treated with ampicillin had a complete recovery/cure. Both therapies reduced body temperature to an afebrile level after two days of treatment. Other variables (depression/malaise, respiratory/dyspnea, nasal discharge) were also assessed during the study; these data further confirmed the efficacy of the treatments.

Bacterial isolates were cultured from transtracheal wash aspirates and/or nasopharyngeal swabs (pretreatment). For the ceftiofur group: 5 horses had both a transtracheal wash (TTW) and a nasopharyngeal swab (NPS), the

remaining 4 horses received only a TTW. Five of the nine TTWs and 4/5 of the NPSs resulted in positive cultures for Streptococcus zooepidemicus. In the ampicillin treatment group, 4 horses had both the TTW and the NPS and the remaining 4 horses had only a TTW. Five of the eight TTWs and 2/4 of the NPSs resulted in positive cultures for Streptococcus zooepidemicus, a total of 10 isolates. Other pathogens isolated were Acinetobacter spp., Actinobacillus spp., Moraxella spp., Pasteurella spp., Staphylococcus spp., and Streptococcus spp. Both therapies were well tolerated: diarrhea was not observed post-treatment, and neither pain nor swelling was observed at the injection sites.

d. Conclusions Regarding Dose Confirmation

Ceftiofur sodium administered SID intramuscularly at 1.0 mg/lb (2.2 mg/kg) of body weight was shown to be safe and efficacious as a therapy for respiratory infections in horses. Diarrhea was not observed post-treatment, and neither pain nor swelling were observed at the ceftiofur injection sites.

B. Corroborative Studies

1. Equine Clinical Study (Ceftiofur vs. Ampicillin)

This was a non-blinded, well-controlled clinical efficacy study in horses with naturally acquired respiratory infections. This study was designed to compare the therapeutic efficacy of ceftiofur sodium (1.0 mg/lb, 2.2 mg/kg; SID) with ampicillin sodium, FDA approved, as the positive control drug at its recommended treatment level of 3 mg/lb (6.6 mg/kg), given BID.

Twenty-nine (29) horses with naturally acquired respiratory infections were included in the study: 15 were treated with ceftiofur and 14 with ampicillin. Both treatments were continued for 48 hours after clinical symptoms were no longer evident (maximum of 10 days). On the basis of pretreatment characteristics, the two treatment groups were comparable. The study was conducted by seven investigators located in CO, FL, KY, MI, MN, TX and VA.

Data from this study indicated ceftiofur sodium was safe and efficacious as a therapy for respiratory infections in horses. Clinical improvement (last day of treatment) was recorded for 13 (87%) of the patients treated with ceftiofur and 13 (93%) of the animals receiving ampicillin. Complete recovery/cure (assessment on the last day of treatment) was noted for 11 (73%) of the ceftiofur patients and 7 (50%) of those treated with ampicillin. Partial recovery was noted for 2 (13%) of the ceftiofur and 6 (43%) of the ampicillin treated animals. Two (13%) of the ceftiofur treated horses and one (7%) ampicillin treated were classified as treatment failures.

At Day 7 post-treatment, 11 (73%) of the ceftiofur patients and 7 (50%) of the horses treated with ampicillin had completely recovered/cured. Partial recovery was noted for 2 (13%) of the ceftiofur group and 5 (36%) of the ampicillin treated group. Treatment failure was noted for 2 (13%) of the ceftiofur group and 2 (14%) of the ampicillin treated horses.

Both therapies reduced body temperature to an afebrile level after two days of treatment. Other variables (depression/malaise, respiration/dyspnea, nasal discharge) were also assessed during the study. These data further confirmed the efficacy of the treatments.

Bacterial isolates were cultured from transtracheal wash aspirates or nasopharyngeal swabs (pretreatment). The most common pathogen cultured from the horses was Streptococcus zooepidemicus (n = 28); other pathogens that were isolated included Streptococcus spp., Pseudomonas spp., Staphylococcus spp., Escherichia spp., Klebsiella spp., Actinobacillus spp., Pasteurella spp., Acinetobacter spp., Serratia spp. and Aeromonas spp.

In conclusion, ceftiofur sodium given SID intramuscularly at 1.0 mg/lb (2.2 mg/kg) of body weight was safe and efficacious as a therapy for respiratory infections in horses. Both treatments were well tolerated: diarrhea was not observed post-treatment and neither pain nor swelling were observed at the injection sites.

III. ANIMAL SAFETY

A. Pivotal Studies

1. Target Animal Safety & Target Animal Tolerance Studies

a. Introduction

Target Animal Tolerance (TAT) and Target Animal Safety (TAS) studies were conducted in horses. The purpose of the TAT study was to demonstrate the potential systemic toxic signs of ceftiofur, and the purpose of the TAS study was to establish the margin of safety of the drug. In the TAT study, ceftiofur sodium was given intravenously to horses at 10 times and 25 times the 1.0 mg/lb (2.2 mg/kg) dose for 10 days. In the TAS study, ceftiofur was given daily for one month at 1, 3 and 5 times the 1.0 mg/lb (2.2 mg/kg) dose. When considering the upper end of the dose range (2.0 mg/lb), ceftiofur sodium was tested at 0.5, 1.5 and 2.5 times the dose.

b. Ten Day Intravenous Target Animal Drug Tolerance Study in Male Horses

Investigators

C.R. Mahrt, DVM, M.A. Klok, W.F. Vogelpohl, M.J. Prough
The Upjohn Company
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The purpose of the Target Animal Drug Tolerance study was to demonstrate the potential systemic toxic signs of ceftiofur sodium in male (gelding) horses following 10 days of daily intravenous infusion of up to 25 times the 1.0 mg/lb dose. This study was conducted in accordance with the GOOD LABORATORY PRACTICES regulation. Twelve adult male (gelding) horses were divided into three groups of four each. Horses in these groups received a single daily intravenous infusion of either 0 mg/lb/day (saline), 10 mg/lb/day, or 25 mg/lb/day of an aqueous solution (50 mg/mL, marketed formulation) of ceftiofur for 10 days. The horses were observed for clinical signs from study days -8 or -7 to 11. Body weights were determined on study days -8 or -7, 1, 6, and 11. Pelleted feed consumption was measured on study days -8 or -7 to 11. Physical examinations were conducted on study days -8 or -7 and 11. Hematology and clinical chemistry parameters were determined on study days -8 or -7, -4, 4, 8, and 11. The horses were euthanized and necropsied on study day 11. Urinalysis was conducted on urine collected at necropsy. Organ weights were determined at necropsy and histopathology was conducted on a complete set of tissues from all horses.

Clinically, intestinal disturbance was detected in both ceftiofur treated groups, but the incidence tended to be greater in the high dose group. The clinical signs included: diarrhea, dehydration, rolling (colic), eating bedding straw, and a dull (inactive, sluggish) demeanor. Decreased pelleted feed consumption was detected in horses from both ceftiofur treated groups, but was more severe in the high dose group. The two horses (one low dose and one high dose) with the most severe diarrhea lost weight during the study.

Hematologic changes related to acute inflammation and stress were detected in both ceftiofur treated groups. The hematologic changes included: increased numbers of white blood cells (segmented and band neutrophils), decreased numbers of lymphocytes, and an increased fibrinogen. Serum chemistry changes related to decreased food consumption and diarrhea were detected from both ceftiofur treated groups. The serum chemistry changes included: decreased concentrations of glucose, urea nitrogen, and albumin, and an increased bilirubin concentration.

Organ weight changes were limited to a mild decrease in the mean absolute and relative liver weights of the high dose group. Drug-related gross pathologic changes were limited to an increase in abdominal fluid in one horse of the low dose group. Drug-related histopathologic changes were detected in the cecum and bone marrow of horses from both ceftiofur treated groups. These histopathologic changes included: submucosal edema and inflammation, excessive mucus and bacteria on the mucosal surface of the cecum, and hyperplasia of the leukocyte series in the bone marrow.

Ceftiofur administered intravenously at a dose of 10 or 25 mg/lb/day changed the bacterial flora of the large intestine leading to inflammation with subsequent diarrhea and other clinical signs. Decreased pelleted feed consumption and a loss of body weight 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.

c. One Month Intramuscular Target Animal Safety Study in Male (Gelding) Horses with a One Month Recovery Period

Investigators
C.R. Mahrt, DVM, M.A. Klok, W.F. Vogelpohl, M.J. Prough
The Upjohn Company
Kalamazoo, MI

This was an acute Target Animal Safety (TAS) study. The purpose of this study was to evaluate the safety of ceftiofur sodium in male (gelding) horses following one month of daily intramuscular injections at 1, 3, and 5 times the 1.0 mg/lb dose. In addition, the horses' ability to reverse any toxic effects within a one month recovery period was evaluated. This study was conducted in accordance with the GOOD LABORATORY PRACTICES regulation.

Twenty (20) adult male (gelding) horses were divided into four groups: six horses in each of the saline control and high dose groups, and four horses in each of the low and intermediate dose groups. Horses in these groups received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1 mg/lb/day (50 mg/mL), 3 mg/lb/day (100 mg/mL), or 5 mg/lb/day (200 mg/mL) [doses are expressed in terms of the free acid ceftiofur] of an aqueous solution for 30 days. Four horses from each group were euthanatized

and necropsied on study day 31 or 32. The remaining horses from the saline control and high dose groups were euthanatized and necropsied on study day 60. The following types of data were collected: clinical observations, physical examinations, pelleted food consumption, body weight, hematology, serum chemistry, urinalysis, organ weights, gross necropsy observations, and histopathology.

A very slight to mild decrease in pelleted food consumption was detected in the horses receiving the 3 and 5 mg/lb/day of ceftiofur. The decreased food consumption began on study day 2 and lasted for approximately nine days. Generally, mild skeletal muscle irritation was detected at the injection sites in all dose groups receiving ceftiofur. The incidence and severity of the muscle irritation tended to increase with each successive increase in the concentration of the dosing solution. Increases in serum concentrations of aspartate aminotransferase(AST, SGOT) and creatine phosphokinase(CPK) were detected in some of the ceftiofur treated horses. The increases were attributed to mild skeletal muscle damage at the injection sites. Edema, reddening, and pallor were observed during gross examination of skeletal muscle at some of the injection sites of the ceftiofur treated horses. Microscopic lesions of hemorrhage, edema, inflammation, separation of muscle fibers, and necrosis were observed at some of the injection sites of the ceftiofur treated horses. The muscle lesions resolved by regeneration of muscle fibers leaving small focal areas of fibrosis.

Ceftiofur sodium was generally well tolerated when administered intramuscularly to male horses at doses up to 5 mg/lb/day for 30 days. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3 and 5 mg/lb/day of ceftiofur sodium and generally mild skeletal muscle irritation at the injection sites of ceftiofur sodium treated horses which resolved by regeneration of muscle fibers and leaving small focal areas of fibrosis. The more severe lesions were associated with the higher concentrations of the dosing solution. This study supports a dosage of 1.0 to 2.0 mg/lb of body weight, a safe treatment level with an adequate margin of safety.

d. One Month Intramuscular Target Animal Safety Study in Female Horses With a One Month Recovery Period

Investigators
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The Upjohn Company
Kalamazoo, MI

This was an acute Target Animal Safety (TAS) study. The purpose of this study was to evaluate the safety of ceftiofur sodium in female horses following one month of daily intramuscular injections at 1, 3, and 5 times the 1.0 mg/lb dose. In addition, the horses' ability to reverse any toxic effects within a one month recovery period was evaluated. This study was conducted in accordance with the GOOD LABORATORY PRACTICES regulation.

Twenty (20) adult female horses were divided into four groups: six horses in each of the saline control and high dose groups, and four horses in each of the low and intermediate dose groups. Horses in these groups received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1 mg/lb/day (50 mg/mL), 3 mg/lb/day (100 mg/mL), or 5 mg/lb/day (200 mg/mL) [doses are expressed in terms of the free acid ceftiofur] of an

aqueous solution for 30 days. Four horses from each group were euthanatized and necropsied on study day 31 or 32. The remaining horses from the saline control and high dose groups were euthanatized and necropsied on study day 60. The following types of data were collected: clinical observations, physical examinations, pelleted food consumption, body weight, hematology, serum chemistry, urinalysis, organ weights, gross necropsy observations, and histopathology.

A very slight to mild decrease in pelleted food consumption was detected in the horses receiving the 3 and 5 mg/lb/day of ceftiofur. The decreased food consumption began on study day 2 and lasted for approximately 12 days. Generally, mild skeletal muscle irritation was detected at the injection sites in all dose groups receiving ceftiofur. The incidence and severity of the muscle irritation tended to increase with each successive increase in the concentration of the dosing solution. Increases in the number of segmented neutrophils in peripheral blood and increases in serum concentrations of aspartate aminotransferase (AST, SGOT), creatine phosphokinase (CPK) and fibrinogen were detected in some of the ceftiofur treated horses and were attributed to mild skeletal muscle damage at some of the injection sites. Reddening and pallor were observed during gross examination of skeletal muscle at some of the injection sites of the ceftiofur treated horses. Microscopic lesions of hemorrhage, edema, inflammation, and necrosis were observed at some of the injection sites of the ceftiofur treated horses. The muscle lesions resolved by regeneration of muscle fibers leaving small focal areas of fibrosis.

Ceftiofur sodium was generally well tolerated when administered intramuscularly to female horses at doses up to 5 mg/lb/day for 30 days. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3 and 5 mg/lb/day of ceftiofur sodium and generally mild skeletal muscle irritation at the injection sites of ceftiofur sodium treated horses which resolved by regeneration of muscle fibers leaving small focal areas of fibrosis. This study supports a dosage of 1.0 to 2.0 mg/lb of body weight, a safe treatment level with an adequate margin of safety.

e. Conclusions Regarding the Safety of Ceftiofur in Horses

In the tolerance study, drug toxicity was observed as expected. None of the horses died, and the adverse effects were most severe within the first few days after dosing was initiated and tended to become less severe toward the end of the 10 day dosing period. In the safety studies, ceftiofur was well tolerated at the 1.0, 3.0 and 5.0 mg/lb dosage levels given daily for one month. Effects that were observed were minimal and transient. The dosage range of 1.0-2.0 mg/lb (2.2-4.4 mg/kg) of body weight given SID intramuscularly was established as being safe for horses.

B. Corroborative Studies

1. P**reliminary Three Day Intravenous Drug Tolerance Study in Male Horses**

Investigators
C.R. Mahrt, M.A. Klok, W.F. Vogelpohl
The Upjohn Company
Kalamazoo, MI

This was a preliminary target animal tolerance study. The purpose of this study was to obtain preliminary data on the potential toxicity of ceftiofur sodium in horses following three daily 25X intravenous doses of the recommended 1.0 mg/lb dose. This study provided preliminary data on the adverse clinical effects of ceftiofur in horses prior to the initiation of the dose determination and field efficacy studies. These data contributed to the design of the definitive drug tolerance and target animal safety studies. These data were not intended for target animal safety evaluation and the study was NOT INSPECTED FOR COMPLIANCE WITH THE GOOD LABORATORY PRACTICES REGULATION.

Six adult male (gelding) horses were divided into two groups of three each. Horses in these groups received intravenous infusions of either 0 mg/lb/day (saline) or 25 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for three days. The horses were observed for clinical signs from study days -3 to 11. Body weights were determined on study days -3, 4, and 11. Pelleted feed consumption was measured on study days -2 to 11. Physical examinations were conducted on study days -3, 4, and 11. Hematology and clinical chemistry parameters were determined on study days -3, 4, and 11. One control horse and one treated horse were euthanatized and necropsied on study day 4. Of the three ceftiofur treated horses, two developed diarrhea and one developed colic. A very slight to severe decrease in pelleted feed consumption and a loss of body weight were also associated with ceftiofur treatment. All three ceftiofur treated horses had an increase in serum bilirubin concentration on study day 4. Increased numbers of neutrophils and decreased numbers of lymphocytes were detected in peripheral blood of all ceftiofur treated horses on study day 4. One of two surviving ceftiofur treated horses also had an increased number of neutrophils in circulating blood on study day 11, and a slight increase in serum fibrinogen on study days 4 and 11. Moderate diffuse edema of the descending colon was observed in the ceftiofur treated horse necropsied on study day 4. Histopathologic examination of this descending colon revealed acute inflammation.

In conclusion, ceftiofur at a dose of 25 mg/lb changes the bacterial flora of the large intestine leading to inflammation of the large intestine with subsequent diarrhea and colic. Decreased pelleted feed consumption and a loss of body weight were also associated with treatment at this dose.

2. Preliminary, Multiple-Dose, Thirty Day Intramuscular Target Animal Safety Study in Horses, With a Thirty Day Recovery Period

Investigators
C.R. Mahrt, M.A. Klok, W.F. Vogelpohl
The Upjohn Company
Kalamazoo, MI

This was a preliminary target animal safety study. The purpose of this study was to obtain preliminary data on the clinical safety of ceftiofur sodium in horses following 30 days of daily intramuscular injection at 5X the 1.0 mg/lb dose and to evaluate the resolution of lesions within a 30 day recovery period. This study provided preliminary data on the adverse clinical effects of ceftiofur in horses prior to the initiation of dose determination and field efficacy studies. These data contributed to the design of definitive drug tolerance and target animal safety studies. These data were not intended for target animal safety evaluation and the study was NOT INSPECTED FOR COMPLIANCE WITH THE GOOD LABORATORY PRACTICES REGULATION.

Twelve (12) adult male (gelding) horses were divided into two groups of six each. Horses in these groups received intramuscular injections of either 0 mg/lb/day (saline) or 5 mg/lb/day of an aqueous ceftiofur sodium solution (150 mg/mL, not the

marketed formulation) for 30 days. The horses were observed for clinical signs from study days -7 to 60. Body weights were determined on study days -7, 1, 11, 21, 31 and 60. Physical examinations were conducted on study days -7, 31, and 60. Hematology and clinical chemistry parameters were determined on study days -7, -4, 11, 31, and 60. Ceftiofur was tolerated when administered to horses at 5 mg/kg for 30 days.

The only definitive drug-related changes detected in this study were increased serum concentrations of creatine phosphokinase (CPK), aspartate aminotransferase (AST, SGOT), and alanine aminotransferase (ALT, SGPT) on study days 11 and 31 which were attributed to mild skeletal muscle damage at the injection sites. The apparent skeletal muscle damage was considered to be mild because the serum enzyme changes were reversible by study day 60 and no swelling or reddening was observed at the injection sites.

In conclusion, ceftiofur was well tolerated when given at 5 mg/lb/day for 30 days. Drug related effects were mild and reversible.

3. Muscular Irritation of Ceftiofur Hydrochloride and Ceftiofur Sodium Following Single Doses of 2.5 mg/lb and 5.0 mg/lb Respectively in Horses - A Preliminary Study

Investigators
A.J. Lallinger, G.M. Baird, J.K. Frecker, R.J. Yancey, Jr.
The Upjohn Company
Kalamazoo, MI

This was a preliminary target animal safety study. The purpose of this study was to determine the gross irritation properties of ceftiofur sodium (200 mg/mL) and ceftiofur hydrochloride (100 mg/mL, experimental formulation) when administered to horses by intramuscular injection. Muscle irritation was evaluated in horses following either a single 2.5 mg/lb intramuscular injection of ceftiofur hydrochloride in cottonseed oil or a single 5.0 mg/lb intramuscular injection of ceftiofur sodium in water for injection.

Six horses were used sequentially for each portion of the study. Adverse effects (pain, itching, edema, swelling or erythema) were not observed following administration of the ceftiofur sodium. Slight swelling was observed at the injection sites of horses treated with ceftiofur hydrochloride at six hours post-treatment. The swelling persisted until 48 hrs post-treatment in two of the horses. Blood samples were collected before and after treatment (until 144 hours post-treatment) and the serum analyzed for changes in creatine kinase (CK) and aspartate aminotransferase (AST). Transient elevations were observed for CK serum levels in animals injected with the ceftiofur salts. The AST serum levels for the horses injected with both formulations remained constant at all sampling periods.

In conclusion, these data suggested ceftiofur hydrochloride in cottonseed oil is slightly irritating when injected into equine muscle, while administration of the sodium salt in water for injection was non-irritating and well tolerated.

IV. DOSE RANGE

A dose range of 1-2 mg/lb body weight per day was established for Naxcel ® . The basis for the dose range is as follows:

There can be considerable variability in an infectious disease from case to case, outbreak to outbreak, and over a period of time. Since respiratory disease in the horse can be acute or chronic and be present in various degrees of severity and with complications, a higher dose may be appropriate in some cases. Target animal safety data indicates that there are no serious adverse effects at 5 mg/lb/day. Therefore, the margin of safety for the upper end of the dose range is greater than 2.5X. Due to the volume necessary to achieve the recommended dosage range (2-4 cc/100 lb body weight), it is unlikely that a dose much higher than 2 mg/lb would be given inadvertently. Therefore it was not considered necessary to conduct a 5X margin of safety study at the 2 mg/lb dose level.

Normally, the Center would require the upper end of the dose range be tested in clinical field trials. However, the safety and efficacy of the upper end of the dose range are established by the following factors: Ceftiofur sodium is approved for use in three other species (bovine, poultry, and swine) and an extensive safety and efficacy data base exists for these species. Ceftiofur is a beta-lactam antibiotic, and this class of antibiotics is well recognized to have a wide margin of safety. Target animal safety studies demonstrate an adequate margin of safety, even for the upper end of the dose range. In summary, due to the data base for this beta-lactam antibiotic drug in other animal species as well as the target species (horse), it was not considered necessary to have tested the 2 mg/lb dose in the field trials.

V. HUMAN SAFETY

A. Human Safety relative to consumption of drug residues:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is approved for use only in horses that are not to be used for food. The product labeling under the heading Residue Warning reads "Not for use in horses intended for food."

B. Human Safety relative to possession, handling, and administration:

When used according to label instructions, the product poses no hazard to the administrator of the product. The Caution statement on the product labeling restricts this drug to use by or on the order of a licensed veterinarian. The label also indicates "Not for human use. Keep out of the reach of children" under the Warning heading. If the user of the product is hypersensitive to the product, the statement under the package insert heading Warning is sufficient to warn those individuals.

VI. AGENCY CONCLUSIONS

The data in support of this supplemental NADA complies with the requirements of Seciton 512 of the Act and Section 514.11 of the implementing regulations. It demonstrates that Naxcel ® Sterile Powder(ceftiofur sodium), when used under labeled conditions of use is safe and effective for the treatment of respiratory infections in horses associated with Streptococcus zooepidemicus.

According to the Center's supplemental approval policy (42 FR 6436), this is a Category II change. This supplement provides for an additional species (equine). The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

The pharmacokinetic and in vitro microbiological data were utilized to support the determination of a effective dose of 1.0 mg/lb; this dose was confirmed to be efficacious and safe for treating respiratory infections in horses in clinical/field studies. The upper

end of the dosage range (2.0 mg/lb) was established on the basis of safety data in the target animal. The recommended dosage range (1.0-2.0 mg/lb) gives the practitioner greater flexibility of using the drug based on his/her clinical judgment.

For the safe and effective use of Naxcel ® Sterile Powder (ceftiofur sodium), it is necessary to provide a diagnosis of respiratory disease in horses which only a trained professional can accomplish. Naxcel is currently a prescription product for use in food animals. We have determined that Naxcel ® Sterile Powder (ceftiofur sodium) remain as a prescription product for use in horses also.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(iii), this approval for non-food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant.

VII. ATTACHMENTS

See attached facsimile vial, carton, and package insert labeling.

Copies of these labels may be obtained by writing to the:
Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.