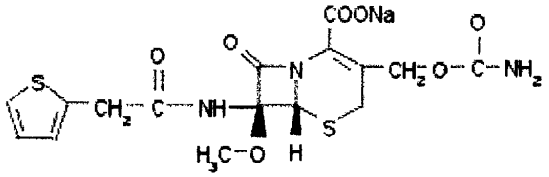
EXHIBIT C

Copy of the Proposed Draft Package Insert for
Cefoxitin for Injection, USP

CEFOXITIN FOR INJECTION, USP

DESCRIPTION

Cefoxitin for Injection, USP is a semi-synthetic, broad-spectrum cepha antibiotic sealed under nitrogen for intravenous administration. It is derived from cephamycin C, which is produced by *Streptomyces lactamdurans*. Its chemical name is sodium (6*R*, 7*S*)-3-(hydroxymethyl)-7-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate carbamate (ester). The empirical formula is $C_{16}H_{16}N_3NaO_7S_2$, and the structural formula is:



Cefoxitin for Injection, USP contains approximately 53.8 mg (2.3 milliequivalents) of sodium per gram of cefoxitin activity. Solutions of Cefoxitin for Injection, USP range from colorless to light amber in color. The pH of freshly constituted solutions usually ranges from 4.2 to 7.0.

CLINICAL PHARMACOLOGY

Clinical Pharmacology

Following an intravenous dose of 1 gram, serum concentrations were 110 mcg/mL at 5 minutes, declining to less than 1 mcg/mL at 4 hours. The half-life after an intravenous dose is 41 to 59 minutes. Approximately 85 percent of cefoxitin is excreted unchanged by the kidneys over a 6-hour period, resulting in high urinary concentrations. Probenecid slows tubular excretion and produces higher serum levels and increases the duration of measurable serum concentrations.

Cefoxitin passes into pleural and joint fluids and is detectable in antibacterial concentrations in bile.

Microbiology

The bactericidal action of cefoxitin results from inhibition of cell wall synthesis. Cefoxitin has *in vitro* activity against a wide variety of gram-positive and gram-negative organisms. The methoxy group in the 7α position provides cefoxitin with a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative bacteria.

Cefoxitin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Staphylococcus aureus[a] (including penicillinase-producing strains)
Staphylococcus epidermidis[a]
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

[a] Staphylococci resistant to methicillin/oxacillin should be considered resistant to cefoxitin.

Most strains of enterococci, e.g., *Enterococcus faecalis*, are resistant.

Aerobic gram-negative microorganisms

Escherichia coli
Haemophilus influenzae
Klebsiella spp. (including *K. pneumoniae*)
Morganella morganii
Neisseria gonorrhoeae (including penicillinase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia spp. (including *Providencia rettgeri*)

Anaerobic gram-positive microorganisms

Clostridium spp.
Peptococcus niger
Peptostreptococcus spp.

Anaerobic gram-negative microorganisms

Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides spp.

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

Cefoxitin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 8 µg/mL or less for aerobic microorganisms and 16 µg/mL or less for anaerobic microorganisms against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefoxitin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms

Eikenella corrodens [non-β-lactamase producers]
Klebsiella oxytoca

Anaerobic gram-positive microorganisms
Clostridium perfringens

Anaerobic gram-negative microorganisms
Prevotella bivia (formerly *Bacteroides bivius*)

Cefoxitin is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae.*

Susceptibility Tests

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefoxitin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms[a,b,c] other than *Neisseria gonorrhoeae*:

MIC (μg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

[a] Staphylococci exhibiting resistance to methicillin/oxacillin should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.
[b] For testing *Haemophilus influenzae* these interpretive criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM)[1].
[c] For testing streptococci these interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1].

For testing *Neisseria gonorrhoeae*[d]:

MIC (μg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

[d] Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[1]. A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reached the concentrations usually achievable. A report of

"Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefoxitin powder should provide the following MIC values:

Microorganism		MIC (µg/mL)
Escherichia coli	ATCC 25922	1-4
Neisseria gonorrhoeae[a]	ATCC 49226	0.5-2
Staphylococcus aureus	ATCC 29213	1-4

[a] Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[1].

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-µg cefoxitin to test the susceptibility of microorganisms to cefoxitin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg cefoxitin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms[a,b,c] other than *Neisseria gonorrhoeae*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

[a] Staphylococci exhibiting resistance to methicillin/oxacillin should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.

[b] For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by disk diffusion method using Haemophilus Test Medium (HTM)[1].

[c] For testing streptococci these interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2[2].

For testing *Neisseria gonorrhoeae*[d]:

Zone Diameter (mm)	Interpretation
≥ 28	Susceptible (S)
24-27	Intermediate (I)
≤ 23	Resistant (R)

[d] Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[2].

Interpretation should be as stated above for results using dilution techniques.

Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefoxitin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg cefoxitin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	23-29
Neisseria gonorrhoeae[a]	ATCC 49226	33-41
Staphylococcus aureus	ATCC 25923	23-29

[a] Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[2].

Anaerobic Techniques:
For anaerobic bacteria, the susceptibility to cefoxitin as MICs can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 16	Susceptible (S)
32	Intermediate (I)
≥ 64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard cefoxitin powder should provide the following MIC values:

Using either an Agar Dilution Method[a] or Using a Broth[b]Microdilution Method:

Microorganism		MIC (µg/mL)
Bacteroides fragilis	ATCC 25285	4-16
Bacteroides thetaiotaomicron	ATCC 29741	8-32

[a] Range applicable only to tests performed using either Brucella blood or Wilkins-Chalgren agar.
[b] Range applicable only to tests performed in the broth formulation of Wilkins-Chalgren agar[3].

INDICATIONS AND USAGE

Treatment

Cefoxitin for Injection, USP is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

1. **Lower respiratory tract infections**, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae,* other streptococci (excluding enterococci, e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, *Haemophilus influenzae,* and *Bacteroides* species.

2. **Urinary tract infections** caused by *Escherichia coli, Klebsiella* species, *Proteus mirabilis, Morganella morganii, Proteus vulgaris* and *Providencia* species (including *P. rettgeri*).

3. **Intra-abdominal infections**, including peritonitis and intra-abdominal abscess, caused by *Escherichia coli, Klebsiella* species, *Bacteroides* species, including *Bacteroides fragilis,* and *Clostridium* species.

4. **Gynecological infections**, including endometritis, pelvic cellulitis, and pelvic inflammatory disease caused by *Escherichia coli, Neisseria gonorrhoeae* (including penicillinase-producing strains), *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, and *Streptococcus agalactiae.* Cefoxitin for Injection, USP, like cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when Cefoxitin for Injection, USP is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

5. **Septicemia** caused by *Streptococcus pneumoniae, Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, and *Bacteroides* species including *B. fragilis.*

6. **Bone and joint infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains).

7. **Skin and structure infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Escherichia coli, Proteus mirabilis, Klebsiella* species, *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger*, and *Peptostreptococcus* species.

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Cefoxitin for Injection, USP. Therapy may be started while awaiting the results of these studies.

In randomized comparative studies, Cefoxitin for Injection, USP and cephalothin were comparably safe and effective in the management of infections caused by gram-positive cocci and gram-negative rods susceptible to the cephalosporins. Cefoxitin for Injection, USP has a high degree of stability in the presence of bacterial beta-lactamases, both penicillinases and cephalosporinases.

Many infections caused by aerobic and anaerobic gram-negative bacteria resistant to some cephalosporins respond to Cefoxitin for Injection, USP. Similarly, many infections caused by aerobic and anaerobic bacteria resistant to some penicillin antibiotics (ampicillin, carbenicillin, penicillin G) respond to treatment with Cefoxitin for Injection, USP. Many infections caused by mixtures of susceptible aerobic and anaerobic bacteria respond to treatment with Cefoxitin for Injection, USP.

Prevention

Cefoxitin for Injection, USP is indicated for the prophylaxis of infection in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.

CONTRAINDICATIONS

Cefoxitin for Injection, USP is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFOXITIN FOR INJECTION, USP IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN,

CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN FOR INJECTION, USP OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefoxitin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis had been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

The total daily dose should be reduced when Cefoxitin for Injection, USP is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

Antibiotics (including cephalosporins) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

As with other antibiotics, prolonged use of Cefoxitin for Injection, USP may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Laboratory Tests

As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions

As with cephalothin, high concentrations of cefoxitin (> 100 micrograms/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction, and produce false increases of modest degree in the levels of creatinine reported. Serum samples from patients treated with cefoxitin should not be analyzed for creatinine if withdrawn within 2 hours of drug administration.

High concentrations of cefoxitin in the urine may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction, and produce false increases of modest degree in the levels reported.

A false-positive reaction for glucose in the urine may occur. This has been observed with CLINITEST† reagent tablets.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed with cefoxitin to evaluate carcinogenic or mutagenic potential. Studies in rats treated intravenously with 400 mg/kg of cefoxitin (approximately three times the maximum recommended human dose) revealed no effects on fertility or mating ability.

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and mice at parenteral doses of approximately one to seven and one-half times the maximum recommended human dose did not reveal teratogenic or fetal toxic effects, although a slight decrease in fetal weight was observed.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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† Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

In the rabbit, cefoxitin was associated with a high incidence of abortion and maternal death. This was not considered to be a teratogenic effect but an expected consequence of the rabbit's unusual sensitivity to antibiotic-induced changes in the population of the microflora of the intestine.

Nursing Mothers

Cefoxitin for Injection, USP is excreted in human milk in low concentrations. Caution should be exercised when Cefoxitin for Injection, USP is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients from birth to three months of age have not yet been established. In pediatric patients three months of age and older, higher doses of Cefoxitin for Injection, USP have been associated with an increased incidence of eosinophilia and elevated SGOT.

ADVERSE REACTIONS

Cefoxitin for Injection, USP is generally well tolerated. The most common adverse reactions have been local reactions following intravenous injection. Other adverse reactions have been encountered infrequently.

Local Reactions

Thrombophlebitis has occurred with intravenous administration.

Allergic Reactions

Rash (including exfoliative dermatitis and toxic epidermal necrolysis), urticaria, flushing, pruritus, eosinophilia, fever, dyspnea, and other allergic reactions, including anaphylaxis, interstitial nephritis and angioedema have been noted.

Cardiovascular

Hypotension

Gastrointestinal

Diarrhea, including documented pseudomembranous colitis, which can appear during of after antibiotic treatment. Nausea and vomiting have been reported rarely.

Neuromuscular

Possible exacerbation of myasthenia gravis

Blood

Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia.

Liver Function

Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase; and jaundice have been reported.

Renal Function

Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of Cefoxitin for Injection, USP in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function usually have been present.

In addition to the adverse reactions listed above, which have been observed in patients treated with Cefoxitin for Injection, USP, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Urticaria, erythema multiforme, Stevens-Johnson syndrome, serum sickness-like reactions, abdominal pain, colitis, renal dysfunction, toxic nephropathy, false-positive test for urinary glucose, hepatic dysfunction including cholestasis, elevated bilirubin, aplastic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, agranulocytosis, superinfection, vaginitis including vaginal candidiasis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See DOSAGE AND ADMINISTRATION.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

The acute intravenous LD_{50} in the adult female mouse and rabbit was about 8.0 g/kg and greater than 1.0 g/kg, respectively. The acute intraperitoneal LD_{50} in the adult rat was greater than 10.0 g/kg.

DOSAGE AND ADMINISTRATION

TREATMENT

Adults

The usual adult dosage range is 1 gram to 2 grams every six to eight hours. Dosage should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient (see Table 1 for dosage guidelines).

If C. *trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefoxitin sodium has no activity against this organism.

Cefoxitin for Injection, USP may be used in patients with reduced renal function with the following dosage adjustments:

In adults with renal insufficiency, an initial loading dose of 1 gram to 2 grams may be given. After a loading dose, the recommendations for *maintenance dosage* (Table 2) may be used as a guide.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\dfrac{\text{Weight (kg)} \times (140\text{-age})}{72 \times \text{serum creatinine (mg/100 mL)}}$

Females: 0.85 x above value

In patients undergoing hemodialysis, the loading dose of 1 to 2 grams should be given after each hemodialysis, and the maintenance dose should be given as indicated in Table 2.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Pediatric Patients

The recommended dosage in pediatric patients three months of age and older is 80 to 160 mg/kg of body weight per day divided into four to six equal doses. The higher dosages should be used for more severe or serious infections. The total daily dosage should not exceed 12 grams.

At this time no recommendation is made for pediatric patients from birth to three months of age (see PRECAUTIONS).

In pediatric patients with renal insufficiency, the dosage and frequency of dosage should be modified consistent with the recommendations for adults (see Table 2).

PREVENTION

Effective prophylactic use depends on the time of administration. Cefoxitin for Injection, USP usually should be given one-half to one hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

For prophylactic use in uncontaminated gastrointestinal surgery, vaginal hysterectomy, or abdominal hysterectomy, the following doses are recommended:

Adults:

2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours.

Pediatric Patients (3 months and older):

30 to 40 mg/kg doses may be given at the times designated above.

Cesarean section patients:

For patients undergoing cesarean section, either a single 2 gram dose administered intravenously as soon as the umbilical cord is clamped OR a 3-dose regimen consisting of 2 grams given intravenously as soon as the umbilical cord is clamped followed by 2 grams 4 and 8 hours after the initial dose is recommended. (See CLINICAL STUDIES.)

Table 1 – Guidelines for Dosage of Cefoxitin for Injection, USP		
Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, cutaneous infection	3-4 grams	1 gram every 6-8 hours IV
Moderately severe or severe infections	6-8 grams	1 gram every 4 hours or 2 grams every 6-8 hours IV
Infections commonly needing antibiotics in higher dosage (e.g., gas gangrene)	12 grams	2 grams every 4 hours or 3 grams every 6 hours IV
* Including patients in whom bacteremia is absent or unlikely.		

Table 2 – Maintenance Dosage of Cefoxitin for Injection, USP in Adults with Reduced Renal Function			
Renal Function	Creatinine Clearance (mL/min)	Dose (grams)	Frequency
Mild impairment	50-30	1-2	every 8-12 hours
Moderate impairment	29-10	1-2	every 12-24 hours
Severe impairment	9-5	0.5-1	every 12-24 hours
Essentially no function	< 5	0.5-1	every 24-48 hours

Table 3 – Preparation of Solution for Intravenous Administration		
Strength	Amount of Diluent to be Added (mL)**	Approximate Average Concentration (mg/mL)
100 gram SmartPak® bag	430 or 930	200 or 100
300 gram SmartPak® bag	1,290 or 2,790	200 or 100
** Shake to dissolve and let stand until clear.		

PREPARATION OF SOLUTION

Table 3 is provided for convenience in constituting Cefoxitin for Injection, USP for intravenous administration.

The 100 gram SmartPak® bags should be constituted with 430 mL of Sterile Water for Injection, USP to yield a final concentration of 200 mg/mL or 930 mL of Sterile Water for Injection, USP to yield a final concentration of 100 mg/mL. The 300 gram SmartPak® bags should be constituted with 1,290 mL Sterile Water for Injection, USP to

yield a final concentration of 200 mg/mL or 2,790 mL of Sterile Water for Injection, USP to yield a final concentration of 100 mg/mL. CAUTION: THE 100 GRAM OR 300 GRAM SMARTPAK® BAGS ARE NOT INTENDED FOR DIRECT INFUSION. The SmartPak® package is for use in a pharmacy admixture service only under a laminar flow hood. Entry into the bag must be made with a sterile transfer set or other sterile dispensing device, and the contents dispensed in aliquots using aseptic technique. The use of syringe and needle is not recommended as they may cause leakage.

ADMINISTRATION

Cefoxitin for Injection, USP may be administered intravenously after constitution.

Parenteral drugs products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent intravenous administration, a solution containing 1 gram or 2 grams in 10 mL of Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. However, during infusion of the solution containing Cefoxitin for Injection, USP, it is advisable to temporarily discontinue administration of any other solutions at the same site.

Solutions of Cefoxitin for Injection, USP, like those of most beta-lactam antibiotics, should not be added to aminoglycoside solutions (e.g., gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction. However, Cefoxitin for Injection, USP and aminoglycosides may be administered separately to the same patient.

COMPATIBILITY AND STABILITY

Cefoxitin for Injection, USP supplied in SmartPak® bags and constituted to concentrations of 100 mg or 200 mg/mL with Sterile Water for Injection maintains satisfactory potency for 6 hours at room temperature or for one week under refrigeration (below 5°C). After the periods mentioned above, any unused solutions should be discarded.

HOW SUPPLIED

Cefoxitin for Injection, USP is a dry, white to off-white powder supplied in a 100-gram plastic bag with foil outer wrap pharmacy bulk package NDC 66288-4100-1 and a 300-gram plastic bag with foil outer wrap pharmacy bulk package NDC 66288-4300-1. Cefoxitin for Injection, USP in the dry state should be stored between 2°-25°C (36°-77°F). Avoid exposure to temperatures above 50°C. The dry material, as well as solutions, tends to darken, depending on storage conditions; product potency, however, is not adversely affected.

CLINICAL STUDIES

A prospective, randomized, double-blind, placebo-controlled clinical trial was conducted to determine the efficacy of short-term prophylaxis with Cefoxitin for Injection, USP in patients undergoing cesarean section who were at high risk for subsequent endometritis because of ruptured membranes. Patients were randomized to receive either three doses of placebo (n=58), a single dose of Cefoxitin for Injection, USP (2 g) followed by two doses of placebo (n=64), or a three-dose regimen of Cefoxitin for Injection, USP (each dose consisting of 2 g) (n=60), given intravenously, usually beginning at the time of clamping of the umbilical cord, with the second and third doses given 4 and 8 hours post-operatively. Endometritis occurred in 16/58 (27.6%) of patients given placebo, 5/63 (7.9%) patients given a single dose of Cefoxitin for Injection, USP, and 3/58 (5.2%) patients given three doses of Cefoxitin for Injection, USP. The differences between the two groups treated with Cefoxitin for Injection, USP and placebo with respect to endometritis were statistically significant ($p<0.01$) in favor of Cefoxitin for Injection, USP. The differences between the one-dose and three-dose regimens of Cefoxitin for Injection, USP were not statistically significant.

Two double-blind, randomized studies compared the efficacy of a single 2 gram intravenous dose of Cefoxitin for Injection, USP to a single 2 gram intravenous dose of cefotetan in the prevention of surgical site-related infection (major morbidity) and non-site-related infections (minor morbidity) in patients following cesarean section. In the first study, 82/98 (83.7%) patients treated with Cefoxitin for Injection, USP and 71/95 (74.7%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: -0.03, +0.21) was not statistically significant. In the second study, 65/75 (86.7%) patients treated with Cefoxitin for Injection and 62/76 (81.6%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: -0.08, +0.18) was not statistically significant.

In clinical trials of patients with intra-abdominal infections due to *Bacteroides fragilis* group microorganisms, eradication rates at 1 to 2 weeks post-treatment for isolates were in the range of 70% to 80%. Eradication rates for individual species are listed below:

Bacteroides distasonis	7/10	(70%)
Bacteroides fragilis	26/33	(79%)
Bacteroides ovatus	10/13	(77%)
B. thetaiotaomicron	13/18	(72%)

REFERENCES

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