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MI: MFXNV:RX1

MEFOXIN®
(CEFOXITIN FOR INJECTION)

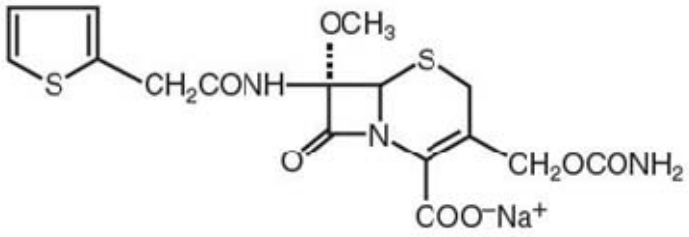
1 g, 2 g and 10 g

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MEFOXIN* and other antibacterial drugs, MEFOXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION: MEFOXIN (cefoxitin for injection) 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 (6R,7S)-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 molecular formula is $C_{16}H_{16}N_3NaO_7S_2$, and the structural formula is:



MEFOXIN contains approximately 53.8 mg (2.3 milliequivalents) of sodium per gram of cefoxitin activity. Solutions of MEFOXIN range from colorless to light amber in color. The pH of freshly constituted solutions usually ranges from 4.2 to 7.0. Each conventional vial contains sterile cefoxitin sodium, USP equivalent to 1 g, 2 g or 10 g cefoxitin.

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.

In a published study of geriatric patients ranging in age from 64 to 88 years with normal renal function for their age (creatinine clearance ranging from 31.5 to 174.0 mL/min), the half-life for cefoxitin ranged from 51 to 90 minutes, resulting in higher plasma

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concentrations than in younger adults. These changes were attributed to decreased renal function associated with the aging process.

Microbiology: ***Mechanism of Action:*** Cefoxitin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefoxitin has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance: Resistance to cefoxitin is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Cefoxitin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE (1) section:

Gram-positive bacteria
- *Staphylococcus aureus* (methicillin-susceptible isolates only)
- *Staphylococcus epidermidis (*methicillin-susceptible isolates only*)*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-negative bacteria
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella* spp.
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia* spp.

Anaerobic bacteria
- *Clostridium* spp.
- *Peptococcus niger*
- *Peptostreptococcus* spp.
- *Bacteroides* spp.

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefoxitin. However, the efficacy of cefoxitin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria
- *Eikenella corrodens* (non-β-lactamase producers)

Anaerobic bacteria
- *Clostridium perfringens*
- *Prevotella bivia*

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Susceptibility Test Methods: When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,3]. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method[2,3]. This procedure uses paper disks impregnated with 30 mcg cefoxitin to test the susceptibility of microorganisms to cefoxitin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Test Interpretive Criteria for Cefoxitin [2,4]

Pathogen	Minimum Inhibitory Concentrations (mcg/mL) [5,6]			Disc Diffusion Diameters (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤ 4	8	≥ 16	Not applicable		
Neisseria gonorrhoeae[a]	≤ 2	4	≥ 8	≥ 28	24 to 27	≤ 23
anaerobic bacteria[b]	≤ 4	8	≥ 16	Not applicable		

Based on a dosing regimen of 2 g every 6 hours
[a]The clinical effectiveness of cefoxitin for treating organisms that produce intermediate results is unknown[2].
[b]Values derived using either *Brucella* blood or Wilkins Chalgren agar are considered equivalent. Values for agar and broth microdilution are considered equivalent[4].

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. 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 antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control: Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individual performing the test[1,2,3,4]. Standard cefoxitin

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powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg disk, the criteria in Table 7 should be achieved.

Table 2. Acceptable Quality Control Ranges for Cefoxitin

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli ATCC 25922	2 to 8	23 to 29
Neisseria gonorrhoeae ATCC 49226	0.5 to 2	33 to 41
Staphylococcus aureus ATCC 25923	---------	23 to 29
Staphylococcus aureus ATCC 29213	1 to 4	---------
Bacteroides fragilis ATCC 25285 (agar method)	4 to 16	---------
Bacteroides fragilis ATCC 25285 (broth method)	2 to 8	---------
Bacteroides thetaiotaomicron ATCC 29741 (agar method)	8 to 32	---------
Bacteroides thetaiotaomicron ATCC 29741 (broth method)	8 to 64	---------
Eubacterium lentum ATCC 43055 (agar method)	4 to 16	---------
Eubacterium lentum ATCC 43055 (broth method)	2 to 16	---------

INDICATIONS AND USAGE: Treatment: MEFOXIN 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.* MEFOXIN, like cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when MEFOXIN 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.

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(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 skin 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 MEFOXIN. Therapy may be started while awaiting the results of these studies.

In randomized comparative studies, MEFOXIN 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. MEFOXIN 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 MEFOXIN. Similarly, many infections caused by aerobic and anaerobic bacteria resistant to some penicillin antibiotics (ampicillin, carbenicillin, penicillin G) respond to treatment with MEFOXIN. Many infections caused by mixtures of susceptible aerobic and anaerobic bacteria respond to treatment with MEFOXIN.

Prevention: MEFOXIN 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MEFOXIN and other antibacterial drugs, MEFOXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS: MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH 'MEFOXIN' IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS,

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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 'MEFOXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Clostridium difficile associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including MEFOXIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C.difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS: General: The total daily dose should be reduced when MEFOXIN 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 MEFOXIN 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.

Prescribing MEFOXIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients: Patients should be counseled that antibacterial drugs including MEFOXIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When MEFOXIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by MEFOXIN or other antibacterial drugs in the future.

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Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting the treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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 3 times the maximum recommended human dose) revealed no effects on fertility or mating ability.

Pregnancy: 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.

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: MEFOXIN is excreted in human milk in low concentrations. Caution should be exercised when MEFOXIN is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients from birth to 3 months of age have not yet been established. In pediatric patients 3 months of age and older, higher doses of

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MEFOXIN have been associated with an increased incidence of eosinophilia and elevated SGOT.

Geriatric Use: Of the 1,775 subjects who received cefoxitin in clinical studies, 424 (24%) were 65 and over, while 124 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

ADVERSE REACTIONS: MEFOXIN 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 or 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 MEFOXIN 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 MEFOXIN, 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

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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 6 to 8 hours. Dosage should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient (see Table 3 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.

MEFOXIN 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 4) 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: $$\frac{\text{Weight (kg) x (140-age)}}{\text{72 x serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value

In patients undergoing hemodialysis, the loading dose of 1 gram to 2 grams should be given after each hemodialysis, and the maintenance dose should be given as indicated in Table 4.

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 3 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.

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At this time no recommendation is made for pediatric patients from birth to 3 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 4).

Prevention: Effective prophylactic use depends on the time of administration. MEFOXIN 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 3. Guidelines for Dosage of MEFOXIN

Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, cutaneous infection	3 to 4 grams	1 gram every 6 to 8 hours IV
Moderately severe or severe infections	6 to 8 grams	1 gram every 4 hours or 2 grams every 6 to 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 4. Maintenance Dosage of MEFOXIN in Adults with Reduced Renal Function

Renal Function	Creatinine Clearance (mL/min)	Dose (grams)	Frequency

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Mild impairment	50 to 30	1 to 2	Every 8 to 12 hours
Moderate impairment	29 to 10	1 to 2	Every 12 to 24 hours
Severe impairment	9 to 5	0.5 to 1	Every 12 to 24 hours
Essentially no function	< 5	0.5 to 1	Every 24 to 48 hours

Table 5. Preparation of Solution for Intravenous Administration

Strength	Amount of Diluent to be Added (mL)**	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
1 gram Vial	10	10.5	95
2 gram Vial	10 or 20	11.1 or 21.0	180 or 95
10 gram Bulk	43 or 93	49 or 98.5	200 or 100

**Shake to dissolve and let stand until clear.

Preparation of Solution: Table 5 is provided for convenience in constituting MEFOXIN for intravenous administration.

For Vials: One gram should be constituted with at least 10 mL, and 2 grams with 10 mL or 20 mL, of Sterile Water for Injection, Bacteriostatic Water for Injection, 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection. These primary solutions may be further diluted in 50 mL to 1000 mL of the diluents listed under the Vials and Bulk Packages portion of the Compatibility and Stability section.

For Bulk Packages: The 10 gram bulk packages should be constituted with 43 mL or 93 mL of Sterile Water for Injection, Bacteriostatic Water for Injection, 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection. CAUTION: THE 10 GRAM BULK STOCK SOLUTION IS NOT FOR DIRECT INFUSION. These primary solutions may be further diluted in 50 mL to 1000 mL of the diluents listed under the Vials and Bulk Packages portion of the Compatibility and Stability section.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than 3 months of age, in whom use of MEFOXIN may be indicated, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity. Therefore, diluent containing benzyl alcohol should not be used when MEFOXIN is constituted for administration to pediatric patients in this age range.

Administration: MEFOXIN may be administered intravenously after constitution.

Parenteral drug 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.

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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 3 to 5 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 MEFOXIN, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For the administration of higher doses by continuous intravenous infusion, a solution of MEFOXIN may be added to an intravenous bottle containing 5 percent Dextrose Injection, 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose and 0.9 percent Sodium Chloride Injection. BUTTERFLY®†† or scalp vein-type needles are preferred for this type of infusion.

Solutions of MEFOXIN, 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, MEFOXIN and aminoglycosides may be administered separately to the same patient.

Directions for Dispensing: ***Pharmacy Bulk Package – Not for Direct Infusion:*** The pharmacy bulk package is for use in a pharmacy admixture service only under a laminar flow hood. Entry into the vial must be made only one time 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 it may cause leakage (see DOSAGE AND ADMINISTRATION). AFTER INITIAL ENTRY USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED WITHIN 4 HOURS.

Compatibility and Stability: ***Vials and Bulk Packages:*** MEFOXIN, as supplied in vials or the bulk package and constituted to 1 gram/10 mL with Sterile Water for Injection, Bacteriostatic Water for Injection, (see Preparation of Solution), 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection, maintains satisfactory potency for 6 hours at room temperature or for one week under refrigeration (below 5°C).

These primary solutions may be further diluted in 50 mL to 1000 mL of the following diluents and maintain potency for an additional 18 hours at room temperature or an additional 48 hours under refrigeration:

0.9 percent Sodium Chloride Injection
5 percent or 10 percent Dextrose Injection
5 percent Dextrose and 0.9 percent Sodium Chloride Injection
5 percent Dextrose Injection with 0.2 percent or 0.45 percent saline solution
Lactated Ringer's Injection
5 percent Dextrose in Lactated Ringer's Injection
5 percent Sodium Bicarbonate Injection
M/6 sodium lactate solution
Mannitol 5% and 10%

After the periods mentioned above, any unused solutions should be discarded.

HOW SUPPLIED: Sterile MEFOXIN is a dry white to off-white powder supplied in vials containing cefoxitin sodium as follows:

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NDC 67457-188-01
1 gram cefoxitin equivalent, in trays of 25 vials

NDC 67457-252-02 –
2 gram cefoxitin equivalent, in trays of 25 vials

NDC 67457-253-10
10 gram cefoxitin equivalent, in trays of 10 bulk vials

Vial stoppers do not contain natural rubber latex.

Special Storage Instructions: MEFOXIN in the dry state should be stored between 2° to 25°C (36° to 77°F). Avoid exposure to temperatures above 50°C. The dry material as well as solutions tend 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 MEFOXIN 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 MEFOXIN (2 g) followed by two doses of placebo (n = 64), or a three-dose regimen of MEFOXIN (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%) patients given placebo, 5/63 (7.9%) patients given a single dose of MEFOXIN, and 3/58 (5.2%) patients given three doses of MEFOXIN. The differences between the two groups treated with MEFOXIN and placebo with respect to endometritis were statistically significant ($p < 0.01$) in favor of MEFOXIN. The differences between the one-dose and three-dose regimens of MEFOXIN were not statistically significant.

Two double-blind, randomized studies compared the efficacy of a single 2 gram intravenous dose of MEFOXIN 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 MEFOXIN 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 MEFOXIN 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 posttreatment 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%)

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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5. Carver PL, Nightingale CH and Quintiliani R. Pharmacokinetics and pharmacodynamics of total and unbound cefoxitin and cefotetan in healthy volunteers. Journal of Antimicrobial Chemotherapy (1989) 23, 99-106

6. CLSI 8 – 11 January 2005 Report (e 284) [Dudley, Jones, Craig and Ambrose]

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