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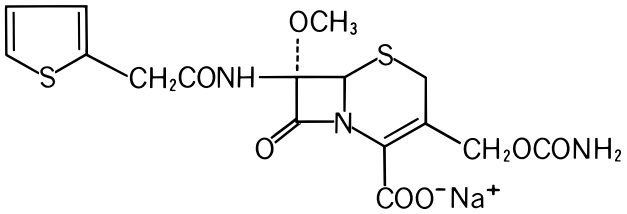
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

MEFOXIN®
(CEFOXITIN FOR INJECTION)

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 (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:



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.

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 range 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*)

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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 (MIC's) 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 (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's 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 interpretative criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM)[1].

[c] For testing streptococci these interpretative 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] Interpretative 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 reaches 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

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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] Interpretative 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 MIC's 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.

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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

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.

(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

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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, 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.

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 has 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 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.

Laboratory Tests

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

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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.

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 three months of age have not yet been established. In pediatric patients three months of age and older, higher doses of MEFOXIN have been associated with an increased incidence of eosinophilia and elevated SGOT.

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.

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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 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.

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

Females: 0.85 x above value

In patients undergoing hemodialysis, the loading dose of 1 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).

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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 1 - 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	3-4 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 MEFOXIN 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 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
1 gram Infusion Bottle	50 or 100	50 or 100	20 or 10
2 gram Infusion Bottle	50 or 100	50 or 100	40 or 20
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 3 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 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 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 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 to 1000 mL of the diluents listed under the *Vials and Bulk Packages* portion of the *COMPATIBILITY AND STABILITY* section.

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Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three 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.

For Infusion Bottles

One or 2 grams of MEFOXIN for infusion may be constituted with 50 or 100 mL of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose Injection.

For ADD-Vantage®†† Vials

See separate INSTRUCTIONS FOR USE OF MEFOXIN IN ADD-Vantage® VIALS. MEFOXIN in ADD-Vantage® vials should be constituted with ADD-Vantage® diluent containers containing 50 mL or 100 mL of either 0.9 percent Sodium Chloride Injection or 5 percent Dextrose Injection. MEFOXIN in ADD-Vantage® vials is for IV use only.

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.

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 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.

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 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%

†† Registered trademark of Abbott Laboratories, Inc.

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Infusion Bottles

MEFOXIN, as supplied in infusion bottles and constituted with 50 to 100 mL of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose Injection, maintains satisfactory potency for 24 hours at room temperature or for 1 week under refrigeration (below 5°C).

ADD-Vantage® Vials

MEFOXIN is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF MEFOXIN IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 50 mL or 100 mL of either 0.9 percent Sodium Chloride Injection or 5 percent Dextrose Injection. When prepared with either of these diluents, MEFOXIN maintains satisfactory potency for 24 hours at room temperature.

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 and infusion bottles containing cefoxitin sodium as follows:

No. 3356 — 1 gram cefoxitin equivalent
NDC 0006-3356-45 in trays of 25 vials.
No. 3357 — 2 gram cefoxitin equivalent
NDC 0006-3357-53 in trays of 25 vials.
No. 3388 — 10 gram cefoxitin equivalent
NDC 0006-3388-67 in trays of 6 bulk bottles.
No. 3548 — 1 gram cefoxitin equivalent
NDC 0006-3548-45 in trays of 25 ADD-Vantage® vials.
No. 3549 — 2 gram cefoxitin equivalent
NDC 0006-3549-53 in trays of 25 ADD-Vantage® vials.

Special storage instructions

MEFOXIN 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 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:

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

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.
3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Fourth Edition. Approved Standard NCCLS Document M11-A4, Vol. 17, No. 22, NCCLS, Villanova, PA, December 1997.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued August 2003
Printed in USA