CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-517/S-031

APPROVED LABELING

APPROVED

7882333

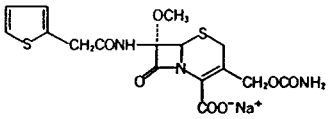
MERCK & CO., INC.
West Point, PA 19486, USA

MEFOXIN®

(STERILE CEFOXITIN SODIUM)

DESCRIPTION

MEFOXIN† (Sterile Cefoxitin Sodium) is a semi-synthetic, broad-spectrum cepha antibiotic sealed under nitrogen for parenteral administration. It is derived from cephamycin C, which is produced by *Streptomyces lactamdurans*. It is the sodium salt of 3-(hydroxymethyl)-7α-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

After intramuscular administration of a 1 gram dose of MEFOXIN to normal volunteers, the mean peak serum concentration was 24 mcg/mL. The peak occurred at 20 to 30 minutes. 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; after intramuscular administration, the half-life is 64.8 minutes. Approximately 85 percent of cefoxitin is excreted unchanged by the kidneys over a 6-hour period, resulting in high urinary concentrations. Following an intramuscular dose of 1 gram, urinary concentrations greater than 3000 mcg/mL were observed. 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.

Clinical experience has demonstrated that MEFOXIN can be administered to patients who are also receiving carbenicillin, kanamycin, gentamicin, tobramycin, or amikacin (see PRECAUTIONS and ADMINISTRATION).

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 MEFOXIN with a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative bacteria. Cefoxitin is usually active against the following organisms *in vitro* and in clinical infections:

Gram-positive

Staphylococcus aureus, including penicillinase and non-penicillinase producing strains
Staphylococcus epidermidis
Beta-hemolytic and other streptococci (most strains of enterococci, e.g., *Streptococcus faecalis*, are resistant)
Streptococcus pneumoniae

Gram-negative

Escherichia coli
Klebsiella species (including *K. pneumoniae*)
Hemophilus influenzae
Neisseria gonorrhoeae, including penicillinase and non-penicillinase producing strains
Proteus mirabilis
Morganella morganii
Proteus vulgaris
Providencia species, including *Providencia rettgeri*

Anaerobic organisms

Peptococcus species
Peptostreptococcus species
Clostridium species
Bacteroides species, including the *B. fragilis* group (includes *B. fragilis*, *B. distasonis*, * *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*)

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

Methicillin-resistant staphylococci are almost uniformly resistant to MEFOXIN.

Susceptibility Tests

For fast-growing aerobic organisms, quantitative methods that require measurements of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs to test susceptibility to cefoxitin. Interpretation involves correlation of the diameters obtained in the disc test with minimal inhibitory concentration (MIC) values for cefoxitin.

Reports from the laboratory giving results of the standardized single disc susceptibility test* using a 30 mcg cefoxitin disc should be interpreted according to the following criteria:

Organisms producing zones of 18 mm or greater are considered susceptible, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15 to 17 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

The cefoxitin disc should be used for testing cefoxitin susceptibility.

Cefoxitin has been shown by *in vitro* tests to have activity against certain strains of *Enterobacteriaceae* found resistant when tested with the cephalosporin class disc. For this reason, the cefoxitin disc should not be used for testing susceptibility to cephalosporins, and cephalosporin discs should not be used for testing susceptibility to cefoxitin.

Dilution methods, preferably the agar plate dilution procedure, are most accurate for susceptibility testing of obligate anaerobes.

A bacterial isolate may be considered susceptible if the MIC value for cefoxitin** is not more than 16 mcg/mL. Organisms are considered resistant if the MIC is greater than 32 mcg/mL.

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., *Streptococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.

(2) **Genitourinary infections.** Urinary tract infections caused by *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive Proteus (which include the organisms now called *Morganella morganii* and *Proteus vulgaris*), and *Providencia* species (including *Providencia rettgeri*). Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

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

(4) **Gynecological infections**, including endometritis, pelvic cellulitis, and pelvic inflammatory disease caused by *Escherichia coli*, *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *Bacteroides fragilis* group***, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and Group B streptococci. 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* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, and *Bacteroides* species including the *Bacteroides fragilis* group.***

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

(7) **Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, streptococci (excluding enterococci e.g., *Streptococcus faecalis*), *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, *Bacteroides* species including the *Bacteroides fragilis* group***, *Clostridium* species, *Peptococcus* species, 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.

* Bauer, A.W.; Kirby, W.M.M.; Sherris, J.C.; Turck, M.: Antibiotic susceptibility testing by a standardized single disc method, Amer. J. Clin. Path. 45: 493-496, Apr. 1966. Standardized disc susceptibility test, Federal Register 37: 20527-20529, 1972. National Committee for Clinical Laboratory Standards: Approved Standard: ASM-2, Performance Standards for Antimicrobial Disc Susceptibility Tests, July 1975.

** Determined by the ICS agar dilution method (Ericsson and Sherris

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.

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.

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

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 virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range from mild to life threatening in severity.

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

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

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), 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.

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

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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 infants from birth to three months of age have not yet been established. In children 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 or intramuscular injection. Other adverse reactions have been encountered infrequently.

Local Reactions

Thrombophlebitis has occurred with intravenous administration. Pain, induration, and tenderness after intramuscular injections have been reported.

Allergic Reactions

Rash (including exfoliative dermatitis and toxic epidermal necrolysis), 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.

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

TREATMENT

Adults

The usual adult dosage range is 1 gram to 2 grams every six to eight hours. Dosage and route of administration 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.

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

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.

The recommended dosage of MEFOXIN for uncomplicated gonorrhea is 2 grams intramuscularly, with 1 gram of BENEMID† (Probenecid) given by mouth at the same time or up to ½ hour before MEFOXIN.

Infants and Children

The recommended dosage in children 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 children from birth to three months of age (see PRECAUTIONS).

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

PREVENTION

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

Adults:

2 grams administered intravenously or intramuscularly 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.

Children (3 months and older):

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

For prophylactic use in vaginal hysterectomy, a single 2.0 gram dose administered intramuscularly one-half to one hour prior to surgery is recommended.

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 or IM
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

assess, since factors predisposing to prerenal azotemia or to impaired renal function usually have been present.

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

TREATMENT

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The usual adult dosage range is 1 gram to 2 grams every six to eight hours. Dosage and route of administration 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.

[1] Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

cutaneous infection		
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

Strength	Amount of Diluent to be Added (mL)**	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
1 gram Vial	2 (intramuscular)	2.5	400
2 gram Vial	4 (intramuscular)	5	400
1 gram Vial	10 (IV)	10.5	95
2 gram Vial	10 or 20 (IV)	11.1 or 21.0	180 or 95
1 gram Infusion Bottle	50 or 100 (IV)	50 or 100	20 or 10
2 gram Infusion Bottle	50 or 100 (IV)	50 or 100	40 or 20
10 gram Bulk	43 or 93 (IV)	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 both intravenous and intramuscular administration.

For intravenous use, 1 gram should be constituted with at least 10 mL of Sterile Water for Injection, and 2 grams, with 10 or 20 mL. The 10 gram bulk package should be constituted with 43 or 93 mL of Sterile Water for Injection or any of the solutions listed under the *Intravenous* portion of the COMPATIBILITY AND STABILITY section. CAUTION: THE 10 GRAM BULK STOCK SOLUTION IS NOT FOR DIRECT INFUSION. One or 2 grams of MEFOXIN for infusion may be constituted with 50 or 100 mL of 0.9 percent Sodium Chloride Injection, 5 percent or 10 percent Dextrose Injection, or any of the solutions listed under the *Intravenous* 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 infants greater than three months of age, in whom use of MEFOXIN may be indicated, small infants 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 infants.

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.

For intramuscular use, each gram of MEFOXIN may be constituted with 2 mL of Sterile Water for Injection, *or* —

For Intramuscular use ONLY: each gram of MEFOXIN may be constituted with 2 mL of 0.5 percent lidocaine hydrochloride solution[‡] (without epinephrine) to minimize the discomfort of intramuscular injection.

ADMINISTRATION

MEFOXIN may be administered intravenously or intramuscularly 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, 5 percent Dextrose and 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection with 0.02 percent sodium bicarbonate solution. 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.

Intramuscular Administration

As with all intramuscular preparations, MEFOXIN should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

[†††] Registered trademark of Abbott Laboratories, Inc.

‡ See package circular of manufacturer for detailed information con-

MEFOXIN® (Sterile Cefoxitin Sodium)

COMPATIBILITY AND STABILITY

Intravenous

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 24 hours at room temperature, for one week under refrigeration (below 5°C), and for at least 30 weeks in the frozen state.

These primary solutions may be further diluted in 50 to 1000 mL of the following solutions and maintain potency for 24 hours at room temperature and at least 48 hours under refrigeration:

Sterile Water for Injection[††]
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 0.02 percent Sodium Bicarbonate solution
5 percent Dextrose Injection with 0.2 percent or 0.45 percent saline solution
Ringer's Injection
Lactated Ringer's Injection[††]
5 percent Dextrose in Lactated Ringer's Injection[††]
5 percent or 10 percent invert sugar in water
10 percent invert sugar in saline solution
5 percent Sodium Bicarbonate Injection
Neut (sodium bicarbonate)[†††††]
M/6 sodium lactate solution
NORMOSOL-M in D5-W[†††††]
IONOSOL B w/Dextrose 5 percent[†††††]
POLYONIC M 56 in 5 percent Dextrose[‡‡‡]
Mannitol 5% and 2.5%
Mannitol 10%[††]
ISOLYTE[§] E
ISOLYTE[§] E with 5% Dextrose

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).

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.

Limited studies with solutions of MEFOXIN in 0.9 percent Sodium Chloride Injection, Lactated Ringer's Injection, and 5 percent Dextrose Injection in VIAFLEX[¶¶] intravenous bags show stability for 24 hours at room temperature, 48 hours under refrigeration or 26 weeks in the frozen state and 24 hours at room temperature thereafter. Also, solutions of MEFOXIN in 0.9 percent Sodium Chloride Injection show similar stability in plastic tubing, drip chambers, and volume control devices of common intravenous infusion sets.

After constitution with Sterile Water for Injection and subsequent storage in disposable plastic syringes, MEFOXIN is stable for 24 hours at room temperature and 48 hours under refrigeration.

After the periods mentioned above, any unused solutions or frozen material should be discarded. Do not refreeze.

Intramuscular

MEFOXIN, as constituted with Sterile Water for Injection, Bacteriostatic Water for Injection, or 0.5 percent or 1 percent lidocaine hydrochloride solution (without epinephrine), maintains satisfactory potency for 24 hours at room temperature, for one week under refrigeration (below 5°C), and for at least 30 weeks in the frozen state.

After the periods mentioned above, any unused solutions or frozen material should be discarded. Do not refreeze.

MEFOXIN has also been found compatible when admixed in intravenous infusions with the following:

Heparin 0.1 units/mL at room temperature — 8 hours
Heparin 100 units/mL at room temperature — 24 hours
M.V.I.[§§§] concentrate at room temperature 24 hours; under refrigeration 48 hours
BEROCCA® C-500 at room temperature 24 hours; under refrigeration 48 hours
Insulin in Normal Saline at room temperature 24 hours; under refrigeration 48 hours
Insulin in 10% invert sugar at room temperature 24 hours; under refrigeration 48 hours

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
(6505-01-119-6005, 1 g 25's).

[††] In these solutions, MEFOXIN has been found to be stable for a period of one week under refrigeration.

[†††] Registered trademark of Cutter Laboratories, Inc.

‡ Registered trademark of American Hospital Supply Corporation.

[§§] Registered trademark of Baxter International, Inc.

No. 3368 — 1 gram cefoxitin equivalent
NDC 0006-3368-71 in trays of 10 infusion bottles
(6505-01-195-0649, 1 g infusion bottle 10's).
No. 3357 — 2 gram cefoxitin equivalent
NDC 0006-3357-53 in trays of 25 vials
(6505-01-104-6393, 2 g 25's).
No. 3369 — 2 gram cefoxitin equivalent
NDC 0006-3369-73 in trays of 10 infusion bottles
(6505-01-185-2624, 2 g infusion bottle 10's).
No. 3388 — 10 gram cefoxitin equivalent
NDC 0006-3388-67 in trays of 6 bulk bottles
(6505-01-263-0730, 10 g 6's).
No. 3548 — 1 gram cefoxitin equivalent
NDC 0006-3548-45 in trays of 25 ADD-Vantage® vials
(6505-01-262-9509, 1 g ADD-Vantage® 25's).
No. 3549 — 2 gram cefoxitin equivalent
NDC 0006-3549-53 in trays of 25 ADD-Vantage® vials
(6505-01-263-4531, 2 g ADD-Vantage® 25's).

Special storage instructions

MEFOXIN in the dry state should be stored below 30°C. 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.

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INSTRUCTIONS FOR USE OF MEFOXIN®* (Cefoxitin for Injection) (Formerly called Sterile Cefoxitin Sodium) IN ADD-Vantage®** VIALS

For IV Use Only.

INSTRUCTIONS FOR USE

To Open Diluent Container:

Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container:

(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening. (SEE FIGURE 1.) Pull the ring approximately half way around the cap and then pull straight up to remove the cap. (SEE FIGURE 2.) NOTE: DO NOT ACCESS VIAL WITH SYRINGE.

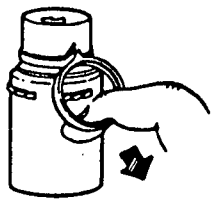

Fig. 1

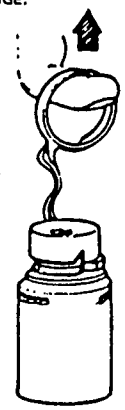

Fig. 2

* Registered trademark of MERCK & CO., Inc.
** Registered trademark of ABBOTT LABORATORIES, Inc.

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   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately ½ turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go. NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)
3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Fig. 3

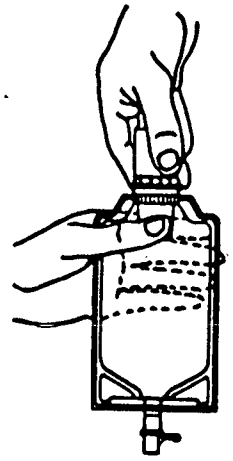

Fig. 4

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

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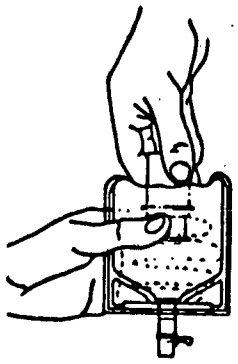

Fig. 5

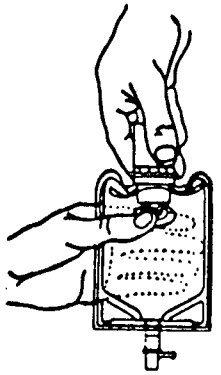

Fig. 6

Preparation for Administration:

(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

Stability

MEFOXIN (Cefoxitin for Injection) 1 gram or 2 gram single dose ADD-Vantage® vials should be prepared with 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 (Cefoxitin for Injection) maintains satisfactory potency for 24 hours at room temperature.

Before administering, see accompanying package circular for MEFOXIN (Cefoxitin for Injection).

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