APPLICATION NUMBER:

50-517/S-039

APPROVAL LETTER
Merck & Co., Inc.
Attention: Henrietta N. Ukwa, M.D.
Director
Regulatory Liaison
P.O. Box 4, BLA-30A
West Point, PA 19486-0004

Dear Dr. Ukwa:

Reference is made to your February 21, 1997 supplemental new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Mefoxin® (sterile cefoxitin for injection).

This supplemental application provides an insert for the ADD-Vantage system to be added to the labeling.

We have completed our review of this submission, and find this supplemental application acceptable. Therefore, the application is approved effective as of the date of this letter.

This approval effects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

If you have any questions concerning this NDA, please contact Mr. Carmen DeBellas, Project Manager, at 301-827-2125.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
APPLICATION NUMBER:

50-517/S-039

APPROVED LABELING
MEFOXIN®
(Sterile Cefoxitin Sodium)

ADMINISTRATION

MEFOXIN may be administered intravenously or intramuscularly after constitution. The bacterial 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 sepsis, or other severe or life-threatening infections, or for patients who may be poor risk because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or metabolic disturbance. Ideally if shock is present or impending.

For intermittent intravenous administration, a solution containing 1gram 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 discontinuous 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 administered in 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.

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, Solvent Less Sterile 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.

The 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, or 5 percent Dextrose 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 lactate solution

NORMOSOL-M in D5W

IONOSOL B w/Dextrose 5 percent

Phosphate buffered 5 percent Dextrose

Mannitol 5 percent

Mannitol 10 percent

ISOLYTE™ E

ISOLYTE™ E w/Dextrose

MEFOXIN, as supplied in infusion bottles and constituted with 50 to 1000 ml of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose.

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

(6505-01-99-90, 1 g 25’s)

No. 3356 — 1 gram cefoxitin equivalent

NDC 0006-3356-71 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

(6505-01-453-92, 2 g 25’s)

No. 3388 — 2 gram cefoxitin equivalent

NDC 0006-3388-71 in trays of 10 infusion bottles

(6505-01-195-0624, 2 g infusion bottle 10’s)

No. 3388 — 2 gram cefoxitin equivalent

NDC 0006-3388-67 in trays of 6 bulk bottles

(6505-01-92-530, 10 g 6’s)

No. 3548 — 1 gram cefoxitin equivalent

NDC 0006-3548-45 in trays of 25 ADD-Vantage® vials

(6505-01-263-9509, 1 g ADD-Vantage® 25’s)

No. 3548 — 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 30°C. The dry material as well as solutions tend to darken, depending on storage conditions; product potency, however, is not adversely affected.

*Registered trademark of Abbott Laboratories, Inc.
†Registered trademark of Baxter International, Inc.
‡Registered trademark of Chas. Pfizer & Co., Inc.
§Registered trademark of Cutter Laboratories, Inc.
¶Registered trademark of American Hospital Supply Corporation.

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©1982 MERCK SHARP & DOHME DIV OF MERCK & CO, INC., WEST POINT, PA 18976 USA
**MEFOXIN®**  
(STERILE CEFOXITIN SODIUM)

**DESCRIPTION**

EFOXIN* (Sterile Cefoxitin Sodium) is a semi-synthetic, broad-spectrum cephalosporin antibiotic sealed under nitrogen for parenteral administration. It is derived from cephemycin C, which is produced by Streptomyces lactacinus. It is the sodium salt of 7-(3-hydroxyethyl)-7a-methoxy-8-oxo-7-[2-(2-nitroacetamido)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (lactamase). The empirical formula is C_{26}H_{33}Na_{2}O_{12}S_{2} and the structural unit is:

![Structural formula of Cefoxitin](image_url)

EFOXIN contains approximately 53.8 mg (2.3 milliequivalents) of sodium gram of cefoxitin activity. Solutions of MEFOXIN range from colorless to amber in color. The pH of freshly constituted solutions usually ranges 4.2 to 7.0.

**CLINICAL PHARMACOLOGY**

**Chemical Pharmacology**

Iver intramuscular administration of a 1 gram dose of MEFOXIN to normal human volunteers the mean peak serum concentration was 24 mg/mL. The peak occurred 20 to 30 minutes. Following an intravenous dose of 1 gram, serum concentrations were 110 mg/mL at 5 minutes, declining to less than 1 mg/mL at 60 minutes. The half-life of this compound is 45 to 56 minutes after intramuscular administration, the half-life is 64.8 hours. Approximately 85% of cefoxitin is excreted unchanged by the kidneys over a 6-hour period, at high urinary concentrations. Following an intramuscular dose of 1 gram, urinary concentrations greater than 3000 mcg/mL were observed. Proecd slows tubular excretion and produces higher serum levels and inures the duration of measurable serum concentrations.

Cefoxitin passes into pleural and joint fluids and is detectable in antibiotics concentrations in bile. Clinical experience has demonstrated that MEFOXIN can be administered to patients also receiving carbencillin, kanamycin, gentamicin, netilmicin, or amikacin (see PRECAUTIONS AND ADMINISTRATION).

**Pharmacology**

The bactericidal action of cefoxitin results from inhibition of cell wall synthesis. Cefoxitin is in vitro activity against a wide range of gram-positive and gram-negative organisms. The methicillin group in the 7a position provides EFOXIN with a high degree of stability in the presence of beta-lactamase production. Cefoxitin is active against the following organisms in vitro and in clinical isolates:

- m-positive tetracycline-resistant strains
- tetracycline-sensitive strains
- streptococcus epidermidis
- beta-lactamases and cephalosporinases of gram-negative bacteria.

Cefoxitin is active against the following organisms in vitro and in clinical isolates:

- m-positive tetracycline-resistant strains
- tetracycline-sensitive strains
- streptococcus epidermidis
- beta-lactamases and cephalosporinases of gram-negative bacteria.

**INDICATIONS AND USAGE**

**Treatment**

MEFOXIN is indicated for the treatment of serious infections caused by strains of the following organisms 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 uncomplicated due to Neisseria gonorrhoeae (penicillinase and non-penicillinase producing).
3. Intraperitoneal infections, including peritonitis and intraperitoneal 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.
5. Bacteremia 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. Skins 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.
8. 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.

**Susceptibility Tests**

For fast-growing aerobic organisms, quantitative methods that require measurement 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 diameter of the zone 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 20 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 dose usage 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.

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**Determined by the IC agar dilution method (Ericsson and Stahria, Acta Path. Microbiol. Scand. [B] Suppl. No. 247, 1971) or any other method that has been shown to give equivalent results.

***B. fragilis, B. dissonans, B. ovatus, B. thetaiotamicron, B. vulgatus.
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 halfway around the cap
        and then pull straight up to remove the cap. (SEE FIGURE 2.)
        NOTE: DO NOT ACCESS VIAL WITH SYRINGE.
    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 in turn (180°) after the first audible click. (SEE FIGURE
        4.) The clicking sound does not mean a seal; the vial must be turned
        4.5 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.

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, do
   not use container 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 twist;
   motion until the pin is firmly seated. NOTE: See full directions
   for administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, bre-
   a. tching the two tie strings. Bend the loop outward to lock it in the up
   b. r. t. position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level
   through the walls of the container. (SEE FIGURE 5.)
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, pilot
   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 0.8 percent Sodium Chloride
Injection or 0.9 percent Dextrose Injection. When prepared with either
these diluents, MEFOXIN® maintains satisfactory potency for 24 hours at room temperature.

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

Issued August 1986
Printed in US
APPLICATION NUMBER:

50-517/S-039

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE
REVIEW OF FINAL PRINTED LABELING (FPL)

APPLICANT: Merck & Co., Inc.
P.O. Box 4, BLA-30A
West Point, PA 19486-0004

DATE OF SUBMISSION: February 21, 1997

DATE OF REVIEW: March 26, 1997

NAMES OF DRUGS:
NDA 50-517 — Mefoxin (sterile cefoxitin sodium)

GENERIC: See above

SUBMISSION HISTORY:
February 21, 1997: The Applicant submitted supplemental application NDA 50-517/S-039 providing instruction for the use of the ADD-Vantage IV system.

Comments: The labeling submitted in this application was compared to labeling for other ADD Vantage products and was found to be acceptable.

RECOMMENDATIONS: An approval letter should be issued.

/S/
Carmen L. DeBellas, PMS

/S/
Janice Soreth, M.D.
CC: Orig NDA 50-517 HFD-520/SCSO/Bona 11/1/97
Concurrence: HFD-520/DIVDIR/Feigal
HFD-520/SMO/Sorenson
HFD-520/DO/Viraragnav
HFD-520/CSO/DeBellas
FPL REVIEW

APPEARS THIS WAY ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hye-Joo Kim
4/26/01 11:08:23 AM
PHARMACIST

Jerry Phillips
4/27/01 09:30:06 AM
DIRECTOR

Martin Himmel
4/27/01 02:29:09 PM
MEDICAL OFFICER

ON ORIGINAL
APPEARS THIS WAY
1. **YES**  
User Fee Cover Sheet Validated?

2. **NO**  
CLINICAL DATA?  
Which TM if containing study reports or literature reports of what are  
educational or independently prepared by the applicant to be adequate and valid  
 overtime evaluation. Clinical data do not include detailed study reports  
listing all or some of the adverse events that would improve the safe use of the drug  
(e.g., to add an adverse reaction, contraindication or warning to the  
labeling).  

KEY: IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL  
DATA ARE CROSS-REFERENCED IN ANOTHER SUBMISSION?

3. **NO**  
NDA being split for administrative convenience (other than  
blinding): If yes, list all NDA numbers, review divisions & indicate those for  
which application fees apply.

4. **NO**  
Blinding policy applied correctly? No data entry required  
for element  
(check TM if application is properly designated as an application or is  
properly submitted as a supplement instead of an original application. then:  
no if application should be apply data more than the application or submitted  
as an NDA. If yes, list all NDA numbers, and  
review divisions.)

5. **YES**  
PRIORITY OR STANDARD?

COPY DISTRIBUTION: GENERAL TO RECEIVED AFTER DATA ENTRY, ONE COPY EACH TO  
DIVISION FEED AND CHEM ASSOCIATE DIRECTOR FOR POLICY 10-5.