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APPLICATION NUMBER:

50-517/S-038

MEDICAL REVIEW

FEB 1 2000

Clinical Review of Supplement

NDA 50-517/S-038

Date of Submission: April 15, 1996

Date of Review: January 29, 1998

Applicant: Merck

Drug - Generic: Cefoxitin
Trade: Mefoxin^{R} (Sterile Cefoxitin Sodium)
Class: Cephalosporin

Related NDA: 50-581/S-027

Route of Administration: IV or IM

Purpose of Submission

The applicant has filed this supplement in accordance with provisions found under 21 CFR 314.70 (b), i.e., supplements that require FDA approval before a change is made. The applicant is responding to the January 26, 1993 letter from the Division of Anti-Infective Drug Products to all NDA holders with regards to revisions in the Microbiology and Susceptibility Tests subsections found under the CLINICAL PHARMACOLOGY section of the labeling.

The submission contains draft labeling with revisions to these subsections, including the addition of new microorganisms, and copies of 61 references from the scientific/medical literature to support these additions.

Review of the Microbiology and Susceptibility Tests Subsections.

The revisions to the Microbiology and Susceptibility Tests subsections of the labeling and the data submitted in support of additional microorganisms were reviewed by Mr. Harold Silver, Microbiologist, HFD-520. (See Clinical Microbiologist Review dated November 24, 1997.) Based on the material submitted, Mr. Silver recommended that these subsections be revised to read as follows:

"***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

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

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

"Aerobic gram-negative microorganisms

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

"Anaerobic gram-positive microorganisms

Clostridium spp.
Peptococcus niger
Peptostreptococcus spp.

"Anaerobic gram-negative microorganisms

Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron

Bacteroides spp.

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

"Cefoxitin exhibits *in vitro* minimum inhibitory concentrations (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 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.

"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]."

II. REFERENCES (Package Insert) subsection

"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 - Third Edition. Approved Standard NCCLS Document M11-A3, Vol 13, No. 26, NCCLS, Villanova, PA, December

1993."

Comments

The reviewers agree with Mr. Silver's recommendations regarding these subsections with one exception. In his review, he deleted *Streptococcus pyogenes* from List #1 concerning microorganisms that are both susceptible to cefoxitin *in vitro* and in which clinical efficacy has been established, i.e., listed under the INDICATIONS AND USAGE section. His basis for this removal was the absence of *Streptococcus pyogenes* or Group A beta-hemolytic streptococci in any of the indications listed in the INDICATIONS AND USAGE section.

Since streptococci are found in two of the currently approved indications (Lower Respiratory Tract Infections and Skin & Skin Structure Infections), it was felt that isolates of *S. pyogenes* or Group A beta-hemolytic streptococci may have been included in the original NDA submission which was reviewed and approved in 1978. The reviewers obtained a copy of the original Medical Officer Review which was written by Dr. George Stanley dated July 17, 1978. In Dr. Stanley's review, there were no isolates of *S. pyogenes* or Group A beta-hemolytic streptococci listed for pathogens isolated from patients with lower respiratory tract infections. There were 12 isolates identified as "other streptococci (excluding group D)" listed for cefoxitin treated patients with this indication.

However, among the cefoxitin treated patients with skin & skin structure infections (SSSI), there were 19 isolates of group A streptococci listed, with 18 of them eradicated (95%) and 29 isolates of "other streptococci (excluding group D)" listed, with 27 of them eradicated (93%). Thus, a sufficient number of *S. pyogenes* isolates were examined to allow the inclusion of this species in the skin & skin structure infection indication and also inclusion in List #1 under the Microbiology subsection. The SSSI indication should be revised for streptococci to read: "*Streptococcus pyogenes* and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis*)." This designation is found in the current labeling for some other cephalosporins, e.g., claforan. This revision should be made to the SSSI indication, while the lower respiratory tract infection indication should remain as is for streptococci.

Review of Submitted Draft Labeling

The draft labeling submitted by the applicant was compared with the latest approved labeling for this product along with revisions requested in recent FDA letters dated April 18, 1995, August 11, 1995, and July 30, 1996. The following changes should be made in order to bring the labeling for this product into compliance with that found for other cephalosporin products.

DESCRIPTION

There are no changes to this section.

CLINICAL PHARMACOLOGY

The third paragraph in the current labeling should be deleted as requested in the FDA letter dated April 18, 1995. It reads:

> "Clinical experience has demonstrated that cefoxitin can be administered to patients who are also receiving amikacin (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.)"

Microbiology

This subsection should be revised according to the recommendations found in the Microbiology review dated November 24, 1997. In addition, *Streptococcus pyogenes* should be added to List #1.

Susceptibility Tests

This subsection should be also be revised according to the recommendations found in the Microbiology review dated November 24, 1997.

INDICATIONS AND USAGE

This section should be revised in accordance with the recommendations found in the Microbiology review regarding name changes for some of the microorganisms. The following changes should be made:

1. Under the Lower respiratory tract infections indication, the words "(including penicillinase-producing strains)" should follow *Staphylococcus aureus*. The words in the current labeling, "(penicillinase- and non-penicillinase-producing)" should be deleted. The other proposed changes for this indication are acceptable.

[ ]

3. In the Intra-abdominal infection indication, the reference to the *B. fragilis* group should be deleted along with the footnote listing the names of four Bacteroides species. The phrase should be changed to read: "Bacteroides species including *Bacteroides fragilis*." This change is necessary to make the wording consistent with that found in the other indications for these species. Also, the *B. fragilis* group presently consists of 10 species, including *B. vulgatus* and *B. uniformis*, for which clinical efficacy with cefoxitin has not been demonstrated. Thus, any reference to the *B. fragilis* group would include these species and would be misleading.

4. Under the Gynecological infections indication, the following changes should be made: The words "(including penicillinase-producing strains)" should replace "(penicillinase- and non-penicillinase-producing)" following *Neisseria gonorrhoeae*; Peptococcus species should be changed to *Peptococcus niger*; and Group B streptococci should be changed to *Streptococcus agalactiae*. The proposed change regarding Bacteroides is acceptable.

5. Under the Septicemia indication, the words "(including penicillinase-producing strains)" should replace "(penicillinase- and non-penicillinase-producing)" following *Staphylococcus aureus*. The proposed change regarding Bacteroides is acceptable.

6. Under the Bone and Joint infections indication, the words "(including penicillinase-producing strains)" should replace "(penicillinase- and non-penicillinase-producing)" following *Staphylococcus aureus*.

7. Under the Skin and Skin Structure infections indication, the following changes should be made: The words "(including penicillinase-producing strains)" should replace "(penicillinase- and non-penicillinase-producing)" following *Staphylococcus aureus*; *Streptococcus pyogenes* should be added to this indication. The phrase should read: "*Streptococcus pyogenes* and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis*.);" and Peptococcus species should be changed to *Peptococcus niger*. The other proposed change regarding Bacteroides species is acceptable.

CONTRAINDICATIONS

There are no changes to this section.

WARNINGS

The last three paragraphs concerning pseudomembranous colitis in the current labeling should be revised as requested in the FDA letter dated April 18, 1995. The paragraphs should read as follows:

> **"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, 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 *C. difficile* colitis."

PRECAUTIONS
ADVERSE REACTIONS
OVERDOSAGE

There are no changes to these sections.

DOSAGE AND ADMINISTRATION

The last subsection heading, STABILITY, should not be in bold type; it is not a section heading.

HOW SUPPLIED

There are no changes to this section.

CLINICAL STUDIES

The paragraph concerning patients with intra abdominal infections due to certain Bacteroides species should be added as specified in the August 11, 1995 FDA letter. The paragraph reads:

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

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

REFERENCES

This section should be revised in accordance with the recommendations found in the Microbiology review. It should read:

"**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 - Third Edition. Approved Standard NCCLS Document M11-A3, Vol 13, No. 26, NCCLS, Villanova, PA, December 1993."

Recommendation

The applicant should be informed of the revisions found in the Microbiology review dated November 24, 1997 and in this review which are necessary to bring the labeling into conformance with the latest approved labeling for cephalosporin drug products. It is recommended that the supplement be approved after the revisions have been made.

/S/

James Blank, Ph.D.

/S/

Holli Hamilton, M.D.

Concurrence Only:
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