CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-517/S-038

MICROBIOLOGY REVIEW

DEC 16 1999

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiological Review

NDA #50-517/SLR-038 **DATE COMPLETED: 11/24/97**

APPLICANT:

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SUBMISSION REVIEWED:
SUPPLEMENT PROVIDING FOR:

Revised draft package insert labeling (#7882333, Issued February 1995) including updated draft labeling on the **CLINICAL PHARMACOLOGY -- Microbiology** and **Susceptibility Tests** subsections, **INDICATIONS AND USAGE** section, and **REFERENCE** section, respectively, on the drug product.

PRODUCT NAMES(S):

Proprietary:	MEFOXIN®
Non-Proprietary/USAN:	cefoxitin sodium
Code Name:	N/A
CAS No.:	*CAS-33564-30-6; CAS-35607-66-0*

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. W.T.:

Cefoxitin sodium:

Chemical Name/Structure	=	See 1996 USAN (Page 137)
Molecular Formula	=	$C_{16}H_{16}N_3NaO_7S_2$
Molecular Weight	=	449.44

DOSAGE FORM: Sterile dried powder stored in either a Vial, Infusion Bottle, ADD-Vantage Vial, or Pharmacy Bulk Vial.

ROUTE OF ADMINISTRATION: Intravenous/Intramuscular

STRENGTH: Cefoxitin sodium equivalent to either 1 g, 2 g, and 10 grams of cefoxitin per container.

PHARMACOLOGICAL CATEGORY:
Cephalosporin (CEPHA Antibiotic Drug)

DISPENSED: ___x___ **Rx** _____ **OTC**

INITIAL SUPPLEMENT SUBMISSION: 4/15/96

AMENDMENT(S): N/A

PATENT: N/A

RELATED DOCUMENTS:

50-517/S-035, Agency's "approvable" letter, filed in Vol. 21.1, and dated 4/18/95.

NDA 50-517/S-028, NDA 50-581/S-015, 50-581/S-016, Agency's "approvable" letter, filed in Vol. 21.1, and dated 8/11/95.

NDA 50-517/S-028, NDA 50-581/S-015, 50-581/S-016, Agency's "approval" letter, filed in Vol. 23.1, and dated 7/30/96.

NDA 50-581, Merck Sharp Dohme, MEFOXIN in Dextrose 5% in single dose GALAXY® Plastic Container (PL 2040) containing either 1 g or 2 g cefoxitin, Approved 9/20/84.

AADA 63-182, Merck, MEFOXIN in Plastic Container containing either 1 g or 2 g cefoxitin, Approved 1/25/93.

COMMENTS:

Original NDA 50-517, MEFOXIN®, cefoxitin sodium equivalent to 1 g, and 2 grams base per vial, respectively. Approved on 1/08/87.

In this submission the applicant has revised and provided draft labeling on the **CLINICAL PHARMACOLOGY -- Microbiology** subsection according to the **NDA Holders Letter**, dated January 26, 1993.

This drug is the subject of the compendial monographs, 21 CFR §442.14a (Sterile cefoxitin sodium), 21 CFR §442.214a (Sterile cefoxitin sodium), and 23 USP (Sterile Cefoxitin Sodium) on pages 304 & 305 respectively.

CONCLUSIONS:

From the microbiological perspective, an "approval" letter should be issued to Merck & Co., Inc., Merck Research Laboratories after negotiation of the revised draft labeling (#7882333), issued February 1995 on the microbiology portion which includes <u>all</u> the Agency's recommendations on the labeling as indicated in **PACKAGE INSERT -- CLINICAL PHARMACOLOGY -- Microbiology** subsection, **Susceptibility Tests** subsection, and the **REFERENCES** section, on pages 51 to 58, and page 59, respectively.

CLINICAL MICROBIOLOGICAL REVIEW

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INTRODUCTION

This supplement, dated 4/15/96, is the applicant's response to the Agency's NDA Holders letter for microbiological labeling information, dated 1/26/93, on the drug product's labeling found in the Package Insert.

Note to Reader:

1. Applicant's most recent revision = Within the strikeout = ~~strikeout~~ (e.g, ~~cefoxitin~~)

2. Microbiologist's revisions = within shaded area = [redline] (e.g., [cefoxitin])

PACKAGE INSERT

(#7882333, Issued February 1995)

The labeling on the **CLINICAL PHARMACOLOGY - Microbiology** and **Susceptibility Tests** subsections, and the **REFERENCES** section should be revised in accordance with the January 26, 1993, letter to all NDA Holders from the Division of Anti-infective Drug Products, as well as recent discussions within the Division and with the applicant. Therefore, the **CLINICAL PHARMACOLOGY - Microbiology** and **Susceptibility Tests** subsections and **REFERENCES** section of the labeling should read as follows:

WITHHOLD 5 PAGE(S)

3. Clinical Microbiology Reviewer's Recommendations:

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[b]

The Beta-hemolytic and other streptococci (most strains of enterococci, e.g, *Enterococcus faecalis*, are resistant)[a]

[redacted]

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

[b] [redacted]

c Beta-hemolytic microorganisms are not mentioned, as so, in the I & U section and "streptococci" should be speciated. Therefore, it is recommended that the labeling statement be revised to read as follows:

"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.

It is recommended that the following labeling statement "MEFOXIN is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae*." be revised and moved from List #1 and be placed at the end of the "in vitro" list (List #2) to read as follows:

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

Microbiologist's Recommendations and Comments on the Microorganisms and Labeling in List #1:

1. Revise the following labeling statement:

"*Staphylococcus aureus*, including penicillinase- and non-penicillinase-producing strains" to read as follows:

Staphylococcus aureus (including penicillinase-producing strains)

To be consistent in the labeling, it is recommended that the Medical Officer also make the aforementioned labeling revision, where appropriate, under the "**INDICATIONS AND USAGE** section.

2. The following labeling statement "Methicillin-resistant staphylococci are almost uniformly resistant to MEFOXIN" should be revised, appropriately placed, and recommended to read as follows:

"Staphylococci resistant to methicillin/oxacillin should be considered resistant to cefoxitin." in reference to both *Staphylococcus aureus* and *Staphylococcus epidermidis*.

3. [redacted]

4. In the following labeling statement "Beta-hemolytic and other streptococci (most strains of enterococci, e.g, *Enterococcus faecalis*, are resistant)":

   "Beta-hemolytic" microorganisms are not mentioned, as so, in the **I & U** section and "streptococci" is a "catchall" term. Therefore, it is recommended that the labeling statement be revised to read as follows:

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

5. Revise the following labeling statement: "*Neisseria gonorrhoeae*, including penicillinase- and non-penicillinase-producing strains" to read as follows:

"*Neisseria gonorrhoeae*, (including penicillinase-producing strains)"

To be consistent in the labeling, it is recommended that the Medical Officer also make the aforementioned labeling revision, where appropriate, under the "**INDICATIONS AND USAGE**" section.

6. *Peptococcus* species should be revised and currently read as follows: *Peptococcus niger*

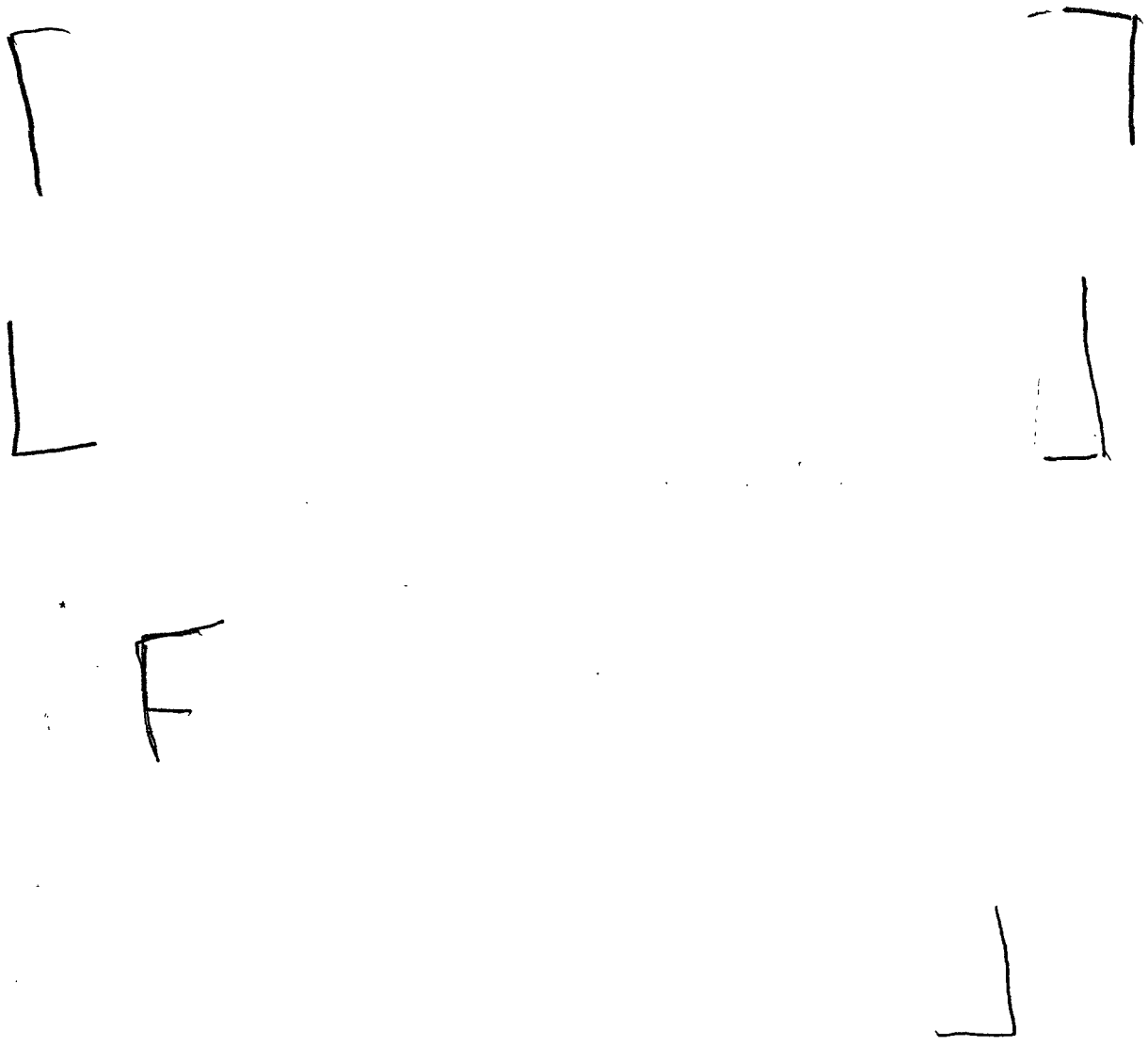
7. The following labeling statement: "MEFOXIN is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae.*" should be revised and read as follows:

"Cefoxitin is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae.*" The labeling statement should be moved from List #1 and be placed at the end of the "in vitro only" list (List #2).

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.

	Potential Pathogen in Approved Infection* or Unknown (?)
Aerobic gram-positive microorganisms	
[redacted]	



DELETION FOOTNOTE REFERENCES (Explanation)

Although the applicant provided extensive literature to support the inclusion of genera and species in List #2 (*in vitro*), the data reviewed and extracted from the literature provided only simple tabulations which described only the geometric mean MIC_{90} values calculated from the literature. The tables reflect only one algorithm of the many that are to be used as described in the NDA Holders letter.

Thus, the applicant is required to present the following information justifying the inclusion of the microorganisms in List #2 (*in vitro*):

1. Scientific evidence should be provided that a microorganism is a pathogen for an approved indication(s) and not anecdotal in nature. Microorganisms associated with severe diseases such as meningitis, TB, brucellosis, leprosy may be included only if specific indications are granted (approved) for these diseases (List #1). Appropriate references, such as the FDA/IDSA guidelines, the FDA Evaluability guidelines and the published literature, should be used to support inclusion in the second list. The number of clinical cases that are available in the published literature and the PK/PD of the drug for the specific site of infection should be taken into consideration when recommending a pathogen for inclusion in the second list. The approved indication(s) along with the causative microorganism(s) (genera and species) should be both identified.

2. At least 90% of the strains tested for each species should be susceptible as defined by the established breakpoint for cefoxitin (at 8 μg/mL or less of cefoxitin for aerobic microorganisms and 16 μg/mL or less of cefoxitin for anaerobic microorganisms), and at least 100 fresh or recent clinical isolates derived from different geographic regions of the United States have been tested and submitted for evaluation.

Since cefoxitin s an approved antiinfective, then the sponsor should provide relevant surveillance data that spans a period of no less than three years and published data that spans a period of no less than 5 years from the date of submission of the document to support inclusion in the second list. For surveillance data, the sponsor should provide the name of the organization conducting the studies, their capabilities, SOPs, and the geographic origin of the database. We would encourage the establishment of a Drug Master File (DMF) for these surveillance facilities. Literature from refereed journals should provide the origin of the data (geographic region , reference lab), test methods used, and methodology quality control to assure the confidence in the data. Publications submitted should provide an overview of MIC ranges, MIC_{50}, and MIC_{90}. NO foreign data will be accepted for antiinfectives marketed in the US.

3. Currently, we discourage the use of "species" as a method for listing microorganism names in the package insert. Therefore, in order to include *Capnocytophaga* spp., *Salmonella* spp., *Shigella* spp., *Mobiluncus* spp., *Eubacterium* spp., and *Veillonella* spp. in the "*in vitro*" list (List #2), the following information must be provided: 1) Documentation that the microorganisms are implicated or recognized as pathogens for the approved indication(s) and 2) that all "species" in that genera are equally susceptible (at 8 μg/mL or less of cefoxitin for aerobic microorganisms and 16 μg/mL or less of cefoxitin for anaerobic microorganisms). For guidance the applicant should refer to the Agency's NDA Holders Letter, dated 1/26/93, including recent recommendations by the Division of Anti-Infective Drug Products (HFD-520).

The following are *in vitro* tabulation susceptibility data, which this Microbiologist's extracted from the literature articles, submitted by the applicant to support the aforementioned requested microorganisms to be included in the "in vitro" list (List #2):

1. **Aerobic Gram-Positive Microorganisms**:

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Staphylococcus saprophyticus						
(67)	(1983)	Canada	10	2	2	13
	(1982)	USA	32	8	16	49
	(1987)	United Kingdom	25	1	2	60

2. **Aerobic Gram-Negative Microorganisms**:

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Aeromonas veronii biovar *sobria*						
(23)	(1990)	Spain	23	1	2	11
Alcaligenes faecalis spp. *faecalis*						
(34)	(1993)	USA	34	4	8	8
Bordetella pertussis						
(60)	(1984)	Canada	60	1.1	2.1	4a
Capnocytophaga spp.						
(96)	(1987)	France	96	0.5	2	4
Citrobacter diversus						
(69)	(1988)	WI, USA	10	8	32	19
	(1989)	CT, USA	9	4	8	30
(1993)		MO/IW/IN/OR/KA, USA	50	≤2	8	44

Aerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Eikenella corrodens [non-β-lactamase producers]						
(100)	(1986)	TN, USA	72	0.5	1	15
	(1980)	NY, USA	28	0.5	0.5	29
Gardnerella vaginalis						
(131)	(1986)	LA, USA	23	≤2.5	2.0	3
	(1993)	CA/WA, USA	15	0.25	2	28
	(1993)	South Africa	93	1	1	38
Haemophilus ducreyi						
(103)	(1982)	South Africa	103	1.0	2.0	7
Helicobacter pylori						
(70)	(1985)	United Kingdom	70	0.12	0.12	41
Klebsiella oxytoca						
(880)	(1988)	WI, USA	10	8	32	19
	(1989)	CT, USA	32	4	8	30
	(1994)	WI, USA	757	≤2	8	43
(1993)		MO/IW/IN/OR/KA, USA	50	≤2	4	44
	(1992)	Saudi Arabia	31	2	16	50
Legionella spp.						
(93)		- References missing -				18/52/58
Moraxella catarrhalis						
(62)	(1989)	CT, USA	14	0.125	0.125	30
1993)		MO/IW/IN/OR/KA, USA	10(BL-)	≤2	≤2	44
	(1993)		23(BRO-1)	≤2	≤2	44
	(1993)		15(BRO-2)	≤2	≤2	44
Neisseria meningitidis						
(41)	(1985)	United Kingdom	16	0.125	0.218	21
	(1981)	OR/IL/KA/CA, USA	25	≤0.12	≤0.12	23
Plesiomonas shigelloides						
(101)	(1990)	NE/CA, USA	29	2	4	12
	(1989)	Canada	72	≤4	≤4	37

Aerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org) (Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Proteus penneri					
(106) (1984)	Canada	45	2	2	24
(1993)	North America	- Information missing -			53
Providencia alcalifaciens					
(81) (1989)	CT, USA	20	2	2	30
(1987)	Italy	61	1.56	3.56	48
Salmonella spp.					
(100) (1985)	United Kingdom	50	1.50	3.56	21
(1984)	MO/IW/IN/OR/KA, USA	50	2	4	24
Shigella spp.					
(172) (1987)	Nigeria	36 (= *S. boydii*)	2	2	20
(1985)	United Kingdom	50	1.80	12.70	21
(1989)	CT, USA	36 (= *S. sonnei*)	2	4	30
(1993)	MO/IW/IN/OR/KA, USA	50	≤2	4	44
Yersinia enterocolitica					
(32) (1989)	USA	32	8	16	30
Yersinia pseudotuberculosis					
(13) (1982)	Spain	13	0.5	1	5

3. **Anaerobic Gram-Positive Microorganisms**:

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Clostridium perfringens						
(272)	(1988)	Australia	44	--	2	14
	(1988)	WI, USA	27	1	2	19
	(1991)	CA, USA	12	2	2	22
	(1993)	CA/PA/WA, USA	12	0.125	2	28
	(1993)	MO/IW/IN/OR/KA, USA	12 (= Mixed)	≤2	16	44
	(1993)	Sweden	30	0.5	1.0	45
	(1993)	North America	88	0.5	0.5	53
	(1994)	PA/OH, USA	20	0.25	1	54
	(1988)	CA, USA	27	--	4	59
Mobiluncus spp.						
(38)	(1993)	CA/PA/WA, USA	16	0.5	1	28
	(1987)	WI, USA (= *M. curtisii*)	12	2	4	55
	(1987)	WI, USA (= *M. mulieris*)	10	0.25	0.5	55
Propionibacterium acnes						
(127)	(1988)	Australia	72	--	0.25	14
	(1993)	Sweden	30	0.125	0.25	45
	(1993)	North America	12	0.125	0.25	53
	(1994)	PA/OH, USA	13	0.25	16	54
Propionibacterium spp.						
(49)	(1993)	CA/PA/WA, USA (*P. acnes* = 10, *P. avidum* = 4, *P. granulosum* = 5)	19	≤0.25	1	28
	(1998)	France (*P. acnes* = 24, *P. avidum* = 4, *P. granulosum* = 2)	30	0.12	0.5	40

4. **Anaerobic Gram-Negative Microorganisms:**

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Bacteroides capillosus						
(29)	(1994)	LA, USA	15	2	8	1
	(1993)	WI, USA	12	2	8	31
(*Prevotella melaninogenica* = 1, *B. buccae* = 2, *B. caccae* = 2, *B. oralis* = 2, *B. capillosus* = 2, *B. uniformis* = 3)						
	(1992)	EUR/USA	14(BL+)	4	16	36
Bacteroides splanchnicus						
(11)	(1993)	North American	11	0.5	1	53
Bacteroides uniformis						
(149)	(1994)	LA, USA	13	4	64	1
	(1992)	Canada	12	8	64	10
	(1988)	WI, USA	22	8	32	19
	(1986)	DE, USA	13	16	32	25
	(1988)	CA, USA	19	8	64	26
	(1993)	CA/PA/WA, USA	12	8	32	28
	(1993)	WI, USA	12	2	8	31
(*Prevotella melaninogenica* = 1, *P. buccae* = 2, *B. caccae* = 2, *B. oralis* = 2, *B. capillosus* = 2, *B. uniformis* = 3)						
	(1992)	USA	26(BL+)	8	16	36
	(1993)	Sweden	- Information missing -			45
	(1991)	Sweden	5(BL+)	8	16	46
	(1991)	Sweden	3(BL-)	8	16	
	(1993)	North America	24	16	32	53
Bacteroides ureolyticus						
(17)	(1992)	EUR/USA	17	4	32	36

Anaerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Bacteroides vulgatus						
(279)	(1994)	LA, USA	33	4	64	1
	(1986)	CANADA	21	4	16	9
	(1988)	WI/USA	35	8	32	19
	(1986)	DE/USA	19	4	16	25
	(1988)	CA/USA	29	8	16	26
	(1993)	CA/PA/WA, USA	10	8	64	28
	(1992)	USA	58 (BL+)	16	32	36
	(1987)	Italy	13	2	4	42
	(1993)	PA/OH, USA	11 (9BL+)	16	32	47
	(1993)	North American	40	8	32	53
	(1994)	PA/OH, USA	10 (10BL+)	16	32	54
Bacteroides spp.						
(112)	(1988)	WI, USA	11	4	8	19
	(1985)	United Kingdom	67	3.79	13.63	21
	(1981)	OR/IL/KA/CA, USA	18	2	8	23
	(*B. melaninogenicus* = 3, *Bactercides* spp. NOS = 15)					
	(1988)	France	16	2	32	40
(*B. asaccharolyticus* = 2, *B. bivius* = 5, *B. multiacidus* = 2, *B. ruminicola* = 7)						
Bilophila wadsworthia						
(56)	(1992)	CA, USA	56	4	4	56
Eubacterium spp.						
(30)	(1994)	LA, USA	18	8	16	1
	(*E. lentum* = 13, *E. limosum* = 4, *E. aerofaciens* = 1)					
	(1988)	WI, USA	12	4	8	19
Fusobacterium mortiferum						
(54)	(1991)	CA, USA	12 (varium group)	8	16	22
	(1992)	EUR/USA	21	4	32	36
	(1993)	North America	21	2	8	53

Anaerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Fusobacterium necrophorum						
(42)	(1988)	WI/USA	- Information missing -			19
	(1993)	PA/OH, USA	12 (2BL+)	0.125	2.0	47
	(1993)	North America	16	0.06	0.25	53
	(1994)	PA/OH, USA	14 (1BL+)	2	4	54
Fusobacterium nucleatum						
(104)	(1991)	CA, USA	12	2	2	22
	(1992)	EUR/USA	17	1	16	36
	(1993)	Sweden	40	0.5	0.5	45
		(*F. nucleatum* = 35, *F. mortiferum* = 3, *F. varium* = 2)				
	(1993)	PA/OH, USA	11 (6BL+)	0.125	32.0	47
	(1993)	North American	13	0.06	1	53
	(1994)	PA/OH, USA	11 (3BL+)	1	2	54
Fusobacterium spp.						
(111)	(1988)	Australia	18	--	32	14
	(1988)	WI, USA	10	2	8	19
	(1991)	CA, USA	33	2	8	22
	(1993)	CA/PA/WA, USA	21	0.25	2	28
		(*F. gonidiaformans* = 1, *F. mortiferum* = 6, *F. necrophorum* = 10, *F. nucleatum* = 4)				
	(1991)	NC, USA	15	0.06	4	34
	(1988)	France	14	0.12	2	40
		(*F. necrophorum* = 5, *F. nucleatum* = 9)				
Porphyromonas asaccharolytica (formerly *Bacteroides asaccharolyticus*)						
(29)	(1985)	NC, USA	9	0.125	0.25	33
	(1991)	Sweden	5 (ML+)	0.5	1.0	46
	(1991)	Sweden	5 (BL-)	0.125	0.5	46
	(1993)	PA/OH, USA	10 (8BL-)	0.25	0.25	47

Anaerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org)	(Lit Publ)	Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Prevotella bivia (formerly *Bacteroides bivius*)						
(372)	(1994)	LA, USA	15	2	8	1
	(1986)	DE, USA	11	≤0.25	32	25
	(1993)	WI, USA	10	0.5	4	31
	(1991)	NC, USA	16	2	4	34
	(1992)	EUR/USA	107(BL+)	≤0.5	8	36
	(1993)	MO/IW/IN/OR/KA, USA	25	≤2	≤2	44
		(*P. bivia, P. disiens*)				
	(1993)	Sweden	50	0.5	1	45
(*Porphyromonas asaccharolytica* = 5, *Prevotella bivia* = 13, *P. disiens* = 12, *P. intermedius* = 5, *P. melaninogenica* = 6, *P. ruminicola* = 9)						
	(1993)	North America	87	0.25	8	53
	(1994)	PA/OH, USA	51(50BL+)	1	16	54
Prevotella disiens (formerly *Bacteroides disiens*)						
(64)	(1994)	LA, USA	13	1	4	1
	(1992)	EUR/USA	18(BL+)	1	16	36
	(1991)	Sweden	13(BL+)	1	2	46
	(1993)	North America	12	0.25	8	53
	(1994)	PA/OH, USA	10(9BL-)	0.5	2	54
Prevotella intermedia (formerly *Bacteroides intermedius*)						
(47)	(1993)	WI, USA	5	0.125	0.5	31
	(1992)	EUR/USA	25(BL+)	2	8	36
	(1993)	Sweden	50	0.5	1.0	45
(*Porphyromonas asaccharolytica* = 5, *Prevotella bivia* = 13, *P. disiens* = 12, *P. intermedia* = 5, *P. melaninogenica* = 6, *P. ruminicola* = 9)						
	(1993)	PA/OH, USA	12(BL+)	1.0	16	47

Anaerobic Gram-Negative Microorganisms (con't):

Microorganism (# Org) (Lit Publ)		Country	No. Strains	MIC_{50}	MIC_{90}	Ref.
Prevotella melaninogenica (formerly *Bacteroides melaninogenicus*)						
(163)	(1984)	LA, USA	37	0.5	4	2
	(1988)	WI, USA	16	0.25	2	19
	(1985)	NC, USA	9	0.5	4	33
	(1992)	EUR/USA	31 (BL+)	4	16	36
	(1991)	Sweden	5 (BL+)	1.0	4	46
	(1991)	Sweden	5 (BL-)	0.25	1	46
	(1993)	PA/OH, USA	12 (BL+)	8	32	47
	(1993)	North America	37	2	16	53
	(1994)	PA/OH, USA	11 (9BL+)	2	16	54
Prevotella spp.						
(167)	(1991)	CA, USA	20	2	2	22
(*P. intermedia* = 9, *P. melaninogenica* = 9, *P. bivia* = 2)						
	(1992)	EUR/USA	10 (BL+)	4	16	36
(*P. loescheii* = 7, *P. buccalis* = 1, *P. corpora* = 1, *P. denticola* = 1)						
	(1992)	EUR/USA	147 (BL-)	≤0.5	4	36
Veillonella spp.						
(39)	(1988)	Australia	29	--	4	14
	(1993)	CA/PA/WA, USA	10	1	2	28

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WITHHOLD 7 PAGE(S)

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* the interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM)[1].

[c] For testing streptococci the 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.

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[d]	ATCC 49226	33-41
Staphylococcus aureus	ATCC 25923	23-29

[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.

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 25235	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 subsection

REFERENCES

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The following Reference should be deleted:

4 [ ]

III. **CONCLUSIONS/RECOMMENDATIONS ON NDA 50-517/SLR-038 (and NDA 50-581/SLR-027 and AADA 63-182):**

From the microbiological perspective, an "approval" letter should be issued to Merck & Co., Inc., Merck Research Laboratories, after negotiation of the revised draft labeling (#7882333, Issued February 1995) on the microbiology portion which includes all the Agency's recommendations on the labeling as indicated in **PACKAGE INSERT -- CLINICAL PHARMACOLOGY -- Microbiology** subsection, **Susceptibility Tests** subsection, and the **REFERENCES** section, to read as follows:

CLINICAL PHARMACOLOGY

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.

/S/

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