

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 50-792

Microbiology Review(s)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
ADDENDUM
TO THE MICROBIOLOGY REVIEW
16 July 2004

NDA 50-792 DATE REVIEW COMPLETED: 24 March 2004

Date Company Submitted: 29 September 2003
Date received by CDER: 02 October 2003
Date Assigned: 08 October 2003

NAME AND ADDRESS OF APPLICANT:

B. Braun Medical Inc.
2525 McGraw Avenue
PO Box 19791
Irvine, CA 92623

CONTACT PERSON:

Qansy Salako, PhD
Director, Regulatory Affairs
Tel: 949-660-2176

DRUG PRODUCT NAME:

Proprietary Name: CLAFORAN®
Established Name: Cefotaxime for Injection

PURPOSE OF SUBMISSION:

The Sponsor, B. Braun, submitted an NDA without clinical data, NDA 50-792, entitled "Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container." B. Braun seeks approval for the same indications as Cefotaxime finished product Claforan, an approved Reference Listed Drug (RLD) for cefotaxime injection. The labeling will be identical to the reference product, except for inclusion of information on the B. Braun DUPLEX® Container / Closure system.

SUMMARY AND RECOMMENDATIONS

The Sponsor, B. Braun, has submitted a copy of an annotated package insert for review. The Microbiology Reviewer provides the following comments and recommendations regarding the Microbiology subsection of the package insert for Cefotaxime, USP for injection and dextrose injection in the Duplex® container provided by the Sponsor.

- Update Quality Control MIC ranges for QC strains of *E. coli*, *P. aeruginosa*, and *S. pneumoniae* to reflect the most current published QC ranges.

- Add a section to reflect

ADDENDUM:

- 1). After further discussion, the Microbiology Reviewer finds the format of the Microbiology subsection of the package insert (product label) proposed by the Sponsor appropriate.
- 2) At this time, a statement that refers to would be deferred.

Connie R. Mahon, MS, CLS_
Microbiologist, HFD-520
16 July 2004

Concurrence:

Peter Coderre, PhD RD#1 initialed 7/23/04, Final initialed, 7/26/04
Acting Microbiology Team Leader
HFD-520

HFD-520/Dept/Dir/L. Gavrilovich

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this page is the manifestation of the electronic signature.**

/s/

Connie Mahon

7/26/04 04:52:44 PM

MICROBIOLOGIST

This is an addendum to the Microbiology Review of
this NDA submission.

Peter Coderre

7/26/04 05:42:15 PM

MICROBIOLOGIST

Lillian Gavrilovich

7/27/04 09:47:32 AM

MEDICAL OFFICER

Product Quality Microbiology Review

Review for HFD-520

12 APRIL 2004

NDA: 50-792

Drug Product Name
Proprietary: Cefotaxime for Injection USP and Dextrose Injection in the Duplex Container
Non-proprietary: Cefotaxime finished Drug Product
Drug Product Classification: Anti-infective

Review Number: 1

Subject of this Review
Submission Date: September 29, 2003
Receipt Date: September 30, 2003
Consult Date: October 20, 2003
Date Assigned for Review: November 03, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): NA
Date(s) of Previous Micro Review(s): NA

Applicant/Sponsor
Name: B. Braun
Address: 25525 McGaw Avenue, Irvine, CA
Representative: Qansy Salako
Telephone: 949-660-2176 FAX 2730

Name of Reviewer: Vinayak B. Pawar

Conclusion: The application is recommended for approval from microbiological standpoint.

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUPPLEMENT: NA
2. SUPPLEMENT PROVIDES FOR: NA
3. MANUFACTURING SITE: Irvine, CA
4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 1 and 2 gram per unit dose, with 50 mL of Dextrose in the diluent chamber.
5. METHOD (S) OF STERILIZATION: ζ \int
6. PHARMACOLOGICAL CATEGORY: Anti-infective
- B. SUPPORTING/RELATED DOCUMENTS: DMF ζ \int
- C. REMARKS: The consult requests the review of an original NDA 50-792 for the drug named Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container. Reference is made to two previously approved B. Braun Duplex products, Cefazolin for injection USP and Cefuroxime for injection USP both with Dextrose Injection USP in the Duplex container. Cefotaxime Sodium, USP, the active ingredient is manufactured in ζ \int the description of which is in DMF ζ \int

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On Original*

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The review of the sterilization validation processes for product, containers and equipment and the results of simulated media fill runs, indicates that the product quality issues are adequately addressed. Therefore, the application is recommended for approval from microbiological standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

Manufacturing of Cefotaxime for Injection USP and Dextrose Injection is performed using

designed for and dedicated to the manufacture of Cephalosporin antibiotic drug products. empty DUPLEX II containers are using equipment manufactured for Braun. All operations for are conducted in

The sterilization The primary processes include:

The secondary processes include

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies - NA

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Vinayak B. Pawar, Reviewer
Peter H. Cooney, Microbiology Supervisor

C. CC Block

cc:
Original NDA 50-792
HFD- 520/Division File/Raquel Peat

7 Page(s) Withheld



 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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/s/

Vinayak Pawar
6/30/04 11:25:03 AM
MICROBIOLOGIST

Peter Cooney
7/6/04 03:08:47 PM
MICROBIOLOGIST

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW**

NDA 50792

DATE REVIEW COMPLETED: 24 March 2004

Date Company Submitted: 29 September 2003

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Date Assigned: 8 October 2003

NAME AND ADDRESS OF APPLICANT:

B. Braun Medical Inc
2525 McGraw Avenue
PO Box 19791
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CONTACT PERSON:

Qansy Salako, PhD
Director, Regulatory Affairs
Tel NO: 949-660-2176

DRUG PRODUCT NAME:

Proprietary Name: CLAFORAN®
Established Name: Cefotaxime for Injection
Code Name:

PURPOSE OF SUBMISSION:

The sponsor, B. Braun, submitted an NDA without clinical data, NDA 50792, entitled "Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container." B Braun seeks approval for the same indications as Cefotaxime finished product Claforan, an approved Reference Listed Drug (RLD) for cefotaxime injection. The labeling will be identical to the reference product, except for inclusion of information on the B. Braun DUPLEX® Container / Closure system.

SUMMARY AND RECOMMENDATIONS

The sponsor, B. Braun, has submitted a copy of an annotated package insert for review. The Microbiology Reviewer provides the following comments and recommendations regarding the Microbiology subsection of the package insert for Cefotaxime, USP for injection and dextrose injection in the Duplex® container provided by the sponsor.

- Update Quality Control MIC ranges for QC strains of *E. coli*, *P.*

aeruginosa, and *S. pneumoniae* to reflect the most current published QC ranges

- Add a section “J” to reflect C

J

REVIEWER’S COMMENTS:

I. GENERAL INFORMATION

The sponsor references two previously approved B Braun Duplex products: Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Container (NDA50779 approved 07/27/2000) and Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX® Container (NDA 50780 approved 02/21/2001) in this application. This NDA application is also referenced to the Agency guidelines and memorandum of meeting minutes for the PRE IND 67 178 during the sponsor’s meeting with the Division on 19 August 2003. There are no microbiology data included in this submission

A. Antimicrobial Spectrum of Activity

Cefotaxime is a semi-synthetic third generation, broad spectrum Cephalosporin and therefore has an expanded spectrum of activity. Cephalosporins, as a class of antimicrobials, are derived from the fermentation of *Acremonium chrysogenum* (formerly designated *Cephalosporium acremonium*). Cephalosporins are grouped by generations that is based generally on their antibacterial activity, i.e. first generation agents are considered to be narrower in spectrum than the later generation compounds.¹

Cefotaxime shows inhibitory activity against 90% of strains of the Enterobacteriaceae including those resistant to aminoglycosides. The activity of cefotaxime against strains of *Serratia marscesens*, *Enterobacter cloacae*, and *Acinetobacter* spp. is variable, therefore bacteriologic culture of clinical samples should be performed to isolate and identify the agent and determine their susceptibilities to cefotaxime. It shows very limited activity against *Pseudomonas aeruginosa*. Table 1 shows a summary of recent surveillance data and published studies of the *in vitro* susceptibility tests results of selected gram-negative species isolated from hospital patients per clinical sample.²

Table 1. Susceptibilities (% susceptible) of Gram negative Bacteria isolated from hospitalized patients with respective clinical infections.²

Organism	UTI	Bacteremia	SSTI	LRT
<i>E. coli</i>	98	98	96.9	92
<i>K. pneumoniae</i>	93	92	92	94
<i>P. mirabilis</i>	99	99	97	99
Other	75			

<i>Serratia</i> spp		86	75	85
<i>Citrobacter</i> spp.		80	75	78
<i>Enterobacter</i> spp		72	70	73
<i>P. aeruginosa</i>		9.3	11.4	12.3
<i>H. influenzae</i>				100

Cefotaxime shows activity against strains of penicillin susceptible *S. pneumoniae* (100%) with an MIC₉₀ of 0.03 µg/mL, while penicillin-resistant *S. pneumoniae* isolates (81.9%) show an MIC₉₀ of 2 µg/mL. This recently published study shows that most pneumococcal isolates that are resistant to penicillin demonstrated lowered susceptibility to extended-spectrum cephalosporins including cefotaxime.³ Additional surveillance data are presented on Tables 2 and 3 from TSN Surveillance Database by Focus Technologies.⁴ The most recent surveillance data on Table 2 (Focus Technologies) shows the in vitro activity of cefotaxime against gram-positive organisms. The bacteriostatic synergistic effect between cefotaxime and amoxicillin against *Enterococcus faecalis* was reported in a paper by Mainardi, JL et al.⁵ Table 3 shows the in vitro activity of cefotaxime against *Providencia* spp., *Salmonella* sp., and *Shigella* spp.

Table 2 *In vitro* Susceptibility Data of Gram-positive organisms taken from TSN Surveillance Database 10/01/1990-11/01/2003⁴

Organism	% Susceptible
<i>Enterococcus faecalis</i>	12.9
<i>Enterococcus faecium</i>	5.6
<i>Staphylococcus aureus</i>	58.1
<i>S. epidermidis</i>	25.2
<i>S. pneumoniae</i>	80.8
<i>S. pyogenes</i>	100
<i>Streptococcus</i> spp	89.7

Table 3 *In vitro* Susceptibility Data of other Gram-negative organisms taken from TSN Surveillance Database 10/01/1990-11/01/2003⁴

Organism	% Susceptible
<i>Providencia</i> spp	90
<i>Salmonella</i> spp	97
<i>Shigella</i> spp	98

B. Mechanism(s) of Action

Cephalosporins interfere with synthesis of peptidoglycan of the bacterial cell wall when they bind to the penicillin-binding proteins of susceptible organisms. Cefotaxime shows in *in vitro* tests bactericidal activity that results from inhibition of cell-wall synthesis.

C. Mechanism(s) of Resistance Studies

Because β -lactam agents such as cephalosporins target penicillin-binding-proteins (PBPs) to interfere in peptidoglycan synthesis, PBP-mediated resistance in usually susceptible bacterial species occurs. PBP-mediated resistance, found predominantly in gram-positive bacteria, takes several forms: acquisition of a foreign PBP with low affinity; recombination of a susceptible PBP with more resistant varieties; and point mutations within PBPs that lower their affinity for the β -lactam antibiotic. Similarly, numerous β -lactamases, a heterogeneous group of proteases have been described. β -lactamases which can be chromosomal, plasmid, or transposon-encoded are secreted into the periplasmic space in gram negative bacteria or into the surrounding environment by gram positive organisms. β -lactamases can be induced or produced constitutively.⁶

Plasmid-mediated β -lactamases (designated as TEM) produced by numerous organisms prompted the pharmaceutical industry to develop new antimicrobial agents resistant to β -lactamase hydrolysis. Of the β -lactamase-resistant antibiotics, the cephalosporin class has been the most successful and widely used, especially the third generation or "extended-spectrum cephalosporins like cefotaxime. This generation of cephalosporins is supposed to be resistant to hydrolysis by TEM. Because of increased clinical use of these agents, however, emergence of extended-spectrum β -lactamases (ESBLs) has been recognized during the last several years. Among the Enterobacteriaceae, ESBLs have been identified mostly in *Klebsiella* spp and *E. coli*, but have also been reported in other species including *Citrobacter*, *Enterobacter*, *Morganella*, *Proteus*, *Providencia*, *Salmonella*, and *Serratia*. Infections caused by ESBL-producing species usually involve patients who are immune compromised in high-risk wards like the intensive care units. The Italian study cited here indicated that 6.3% of Enterobacteriaceae harbor ESBL genes. The prevalence and types of ESBLs varied according to species. The table below shows susceptibilities to cefotaxime by species and ESBL gene-type.⁷

Table 4 Susceptibilities to Cefotaxime by Species and ESBL- gene Types

Species	ESBL gene-type	MIC ₅₀	MIC ₉₀
<i>P. mirabilis</i>	TEM	8	16
<i>P. stuartii</i>	TEM	8	16
<i>K pneumoniae</i>	TEM	4	32
	SHV	8	32
	TEM and SHV	8	32
	Non-TEM/ non-SHV	8	32
<i>E. coli</i>	TEM	8	16
	SHV	4	32
<i>E aerogenes</i>	TEM	8	16
	SHV	16	32

D. Susceptibility Interpretive Criteria for Cefotaxime

The table below shows the susceptibility interpretive criteria for cefotaxime as presented in the annotated (copy) package insert provided by the sponsor.

Table 5 Susceptibility Interpretive Criteria for Cefotaxime

Pathogen	Susceptibility Test Result Interpretive Criteria					
	Minimal Inhibitory Concentrations ^a (ug/mL)			Disk Diffusion ^a (zone diameters in mm)		
	S	I	R	S	I	R
<i>Streptococcus</i> spp ^{b, c}	≤0.5	1	>2	≥28	26-27	≤28
<i>Neisseria gonorrhoeae</i> ^d	≤0.5	-	-	≥31	-	-
<i>Haemophilus influenzae</i> ^e	≤2.0	-	-	≥26	-	-
Organisms ^f other than <i>Haemophilus</i> spp or <i>Neisseria gonorrhoeae</i> Or <i>Streptococcus</i> spp.	≤8	16-32	≥64	≥23	15-22	≤14
Anaerobic organisms ^g	≤16	32	≥64	-	-	-

^a The current absence of data on resistant strains precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

^b These zone diameter standards apply to susceptibility tests using cat-ion adjusted Mueller-Hinton agar 5% defibrinated sheep blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C, 5% CO₂ for 20-24 hours.

^c These interpretive standards are applicable only to broth susceptibility tests using cat-ion adjusted Mueller-Hinton broth with 2-5% lysed horse blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; ambient air; for 20-24 hours.

^d Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement

^e These interpretive standards are applicable only to broth susceptibility tests with *H. influenzae* using Haemophilus Testing Medium (HTM); an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; % CO₂; for 16-18 hours.

^f Staphylococci which are resistant in methicillin/oxacillin must be considered resistant to cefotaxime sodium despite apparent in vitro susceptibility.

^g Ranges apply only to tests performed by agar dilution method.

E. Quality Control Parameters

Routine quality control procedures involve performance testing of designated quality control strains that are genetically stable and have well-characterized susceptibility characteristics. The reference strains (Table 6) used by the sponsor were those recommended by the NCCLS documents. However, recently published NCCLS documents show updated MICs for *E. coli*, *P. aeruginosa*, and *S. pneumoniae*. The microbiology reviewer recommends that the acceptable quality control ranges for cefotaxime reflect the most current QC ranges.^{9,10}

Table 6 Acceptable Quality Control Ranges for Cefotaxime

Acceptable Quality Control Ranges

QC Strain		Minimum Inhibitory ($\mu\text{g/mL}$)	Disk Diffusion (Zone diameter in mm)
<i>E. coli</i>	ATCC 25922	0.06-0.25	(0.03-0.12) *
<i>S aureus</i>	ATCC 29213	1-4	Not applicable
<i>S aureus</i>	ATCC 25923	Not applicable	25-31
<i>S. pneumoniae</i>	ATCC 49619 ^h	0.06-0.25	(0.03-0.12) *
<i>P. aeruginosa</i>	ATCC 27853	4-16	(8-32)*
<i>H. influenzae</i>	ATCC 49247 ⁱ	0.12-0.5	31-39
	⌊		⌋
<i>Bacteroides fragilis</i>	ATCC 25285 ^k	8-32	-
<i>Bacteroides thetaiotaomicron</i>	ATCC 29741 ^k	16-64	-
<i>Eubacterium lantem</i>	ATCC 43055 ^k	64-256	-

* Current QC MIC acceptable ranges^{9,10}

^hThis quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cat-ion adjusted Mueller-Hinton broth with 2-5% lysed horse blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; ambient air; for 20-24 hours.

ⁱThis quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension; incubation at 35°C, 5% CO₂ for 16 to 18 hours.

⌊

⌋

^kRanges apply only to tests performed by agar dilution method.

RECOMMENDED Microbiology Subsection of the Package Insert

The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Cefotaxime sodium has a high degree of stability in the presence of β -lactamases, both penicillinases and cephalosporinases of gram-negative and gram-positive bacteria. Cefotaxime 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.

Aerobes, Gram-positive: *Enterococcus* spp., *Staphylococcus aureus**, including (beta)-lactamase-positive and negative strains, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), and *Streptococcus* spp.

*Staphylococci which are resistant in methicillin/oxacillin must be considered resistant to cefotaxime sodium.

Aerobes, Gram-negative: *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*, *Klebsiella* spp. (including *Klebsiella pneumoniae*), *Morganella morganii*, *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, and *Serratia marcescens*.

Note: Many strains of the above organisms that are multiply resistant antibiotics, e.g. penicillins, cephalosporins, and aminoglycosides, are susceptible to cefotaxime sodium. Cefotaxime sodium is active against some strains of *Pseudomonas aeruginosa*.

Anaerobes: *Bacteroides* species, including some strains of *Bacteroides fragilis*, *Clostridium* spp. (NOTE: Most strains of *Clostridium difficile* are resistant), *Fusobacterium* spp. (including *Fusobacterium nucleatum*), *Peptococcus* spp., and *Peptostreptococcus* spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MIC's) at 8 µg/mL or less against most (>/=90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:

Providencia spp., *Salmonella* spp. (including *Salmonella typhi*), and *Shigella* spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of β-lactamases described by Richmond et al.¹, including Type IIIa (TEM) which is produced by many gram-negative bacteria. The drug is also stable to β-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP:1b and III.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests:

When available, the results of in vitro susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine minimum inhibitory concentrations (MICs) estimates of the susceptibility of bacteria to antimicrobial compounds. using a standardized procedure. Standardized procedures are based on a dilution method^{2,3} (broth or agar) or equivalent with cefotaxime powder. The MIC values should be interpreted according to criteria

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 procedure⁴ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with cefotaxime to test the susceptibility of microorganisms to cefotaxime.

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to cefotaxime as MICs can be determined by a standardized test method.⁶ The MIC values obtained should be interpreted according to the criteria

Table 1 Susceptibility Interpretive Criteria for Cefotaxime

Susceptibility Test Result Interpretive Criteria						
Pathogen	Minimal Inhibitory Concentrations ^a (ug/mL)			Disk Diffusion ^a (zone diameters in mm)		
	S	I	R	S	I	R
<i>Streptococcus</i> spp ^{b,c}	≤0.5	1	>2	≥28	26-27	≤28
<i>Haemophilus influenzae</i> ^e	≤2.0	-	-	≥26	-	-
Organisms ^f other than <i>Haemophilus</i> spp or						

Or <i>Streptococcus</i> spp.	≤8	16-32	≥64	≥23	15-22	≤14
Anaerobic organisms ^g	≤16	32	≥64	-	-	-

- ^a The current absence of data on resistant strains precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
- ^b These zone diameter standards apply to susceptibility tests using cat-ion adjusted Mueller-Hinton agar 5% defibrinated sheep blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C, 5% CO₂ for 20-24 hours.
- ^c These interpretive standards are applicable only to broth susceptibility tests using cat-ion adjusted Mueller-Hinton broth with 2-5% lysed horse blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; ambient air; for 20-24 hours.
- ^d []
- ^e These interpretive standards are applicable only to broth susceptibility tests with *H. influenzae* using Haemophilus Testing Medium (HTM); an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; % CO₂; for 16-18 hours.
- ^f Staphylococci which are resistant in methicillin/oxacillin must be considered resistant to cefotaxime sodium despite apparent in vitro susceptibility.
- ^g Ranges apply only to tests performed by agar dilution method.

If there is no "Resistant" criteria due to the lack of data on resistant microorganisms then the following should be noted in the package labeling: "The current absence of data on resistant strains precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing."

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 that 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.

QUALITY CONTROL

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard cefotaxime powder should provide the following range of values noted in Table 2. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains that will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 2. Acceptable Quality Control Ranges for Cefotaxime

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory ($\mu\text{g/mL}$)	Disk Diffusion (Zone diameter in mm)
<i>E. coli</i> ATCC 25922	0.03-0.12	29-35
<i>S aureus</i> ATCC 29213	1-4	Not applicable
<i>S aureus</i> ATCC 25923	Not applicable	25-31
<i>S. pneumoniae</i> ATCC 49619 ^h	0.03-0.12	-
<i>P. aeruginosa</i> ATCC27853	8-32	18-22
<i>H. influenzae</i> ATCC 49247 ⁱ	0.12-0.5	31-39
<i>Bacteroides fragilis</i> ATCC 25285 ^k	8-32	-
<i>Bacteroides thetaiotaomicron</i> ATCC 29741 ^k	16-64	-
<i>Eubacterium lantem</i> ATCC 43055 ^k	64-256	-

^h This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cat-ion adjusted Mueller-Hinton broth with 2-5% lysed horse blood; an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension incubation at 35°C; ambient air; for 20-24 hours.

ⁱ This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM¹ an inoculum size equivalent to a 0.5 McFarland standard using a direct colony suspension; incubation at 35°C, 5% CO₂ for 16 to 18 hours.

^k Ranges apply only to tests performed by agar dilution method.

References:

- ¹Richmond, MH and Sykes, RB. The b-lactamases of gram-negative bacteria and their possible physiological role. 1973. *Advances in Microbial Physiology*.9:31-88.
- ² National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* –Approved Standard 6th Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2 (ISBN 1- 56238 – 486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA19087-1898, January, 2003.
- ³ National Committee for Clinical Laboratory Standards. MIC Testing Supplemental Tables NCCLS Document M100- S13 (ISBN 1-56238-485-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
- ⁴ National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* – 8th Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1 (ISBN 1-56238 – 485-6). NCCLS, 940 West Valley Road, Wayne, PA 19087-1898, January, 2003.
- ⁵ National Committee for Clinical Laboratory Standards. *Disk Diffusion Supplemental Tables* NCCLS Document M100- S13(M2) (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
- ⁶ National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*– 5th Edition. Approved Standard NCCLS Document M11-A5, Vol. 21, No. 2 (ISBN 1- 56238 – 485-6). NCCLS, 940 West Valley Road, Wayne, PA 19087-1898, January, 2003.

CONCLUSION AND RECOMMENDATIONS

The sponsor, B. Braun, has submitted a copy of an annotated package insert for review. The Microbiology Reviewer is providing the following comments and

recommendations regarding the Microbiology subsection of the package insert for Cefotazime, USP for injection and dextrose injection in the Duplex® container provided by the sponsor.

- Update Quality Control MIC ranges for QC strains of *E. coli*, *P. aeruginosa*, and *S. pneumoniae* to reflect the most current published QC ranges.
- Add a section to reflect

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Microbiologist, HFD-520
24 March 2004

Concurrence:

HFD-520/Dept/Dir/L. Gavrilovich

References:

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² Wenzel RP et al. In vitro susceptibilities of Gram-negative bacteria from hospitalized patients in four European Countries: Canada, and the United States in 2000-01 to expanded-spectrum cephalosporins and comparator antimicrobials: implications for therapy.

³ Karlowsky, et al. Clinical Isolates of *Streptococcus pneumoniae* with different susceptibilities to ceftriaxone and cefotaxime. 2003. *Antimicrob Agents and Chemo.* 47:3155-3160.

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⁵ Mainardi JL et al Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. 1995. *Antimicrob Agents and Chemo.* 39:1984-1987.

⁶ Rice, LB, Sahm, D. and Bonomo, R. Mechanisms of resistance to antimicrobial agents. A chapter in *Manual of Clinical Microbiology*, 8th ed. Murray, P. et al eds. American Society for Microbiology. Washington DC. 2003. pages 1074-1101.

⁷ Spanu T. et al Occurrence of Extended-spectrum β -lactamases in members of the family Enterobacteriaceae in Italy: Implication for resistance to β -lactams and other antimicrobial drugs. 2002. *Antimicrob Agents and Chemo.* 46:196-202.

⁸ Richmond, MH and Sykes, RB. The β -lactamases of gram-negative bacteria and their possible physiological role. 1973. *Advances in Microbial Physiology.* 9:31-88.

⁹ National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* – Approved Standard 6th Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2 (ISBN 1- 56238 – 486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.

¹⁰ National Committee for Clinical Laboratory Standards. MIC Testing Supplemental Tables NCCLS Document M100- S13 (ISBN 1-56238-485-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.

¹¹ National Committee for Clinical Laboratory Standards. Disk Diffusion Supplemental Tables NCCLS

Document M100- S13(M2) (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.

¹² National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* – 8th Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1 (ISBN 1-56238 – 485-6). NCCLS, 940 West Valley Road, Wayne, PA 19087-1898, January, 2003.

¹³ National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*– 5th Edition. Approved Standard NCCLS Document M11-A5, Vol. 21, No. 2 (ISBN 1- 56238 – 485-6). NCCLS, 940 West Valley Road, Wayne, PA 19087-1898, January, 2003.

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