CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-780

MICROBIOLOGY REVIEW

DEC 4 2000

Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE
50780	11-20-00	Original NDA

DOCUMENT DATE	CDER DATE	ASSIGNED DATE
4-17-00	4-24-00	4-27-00

NAME & ADDRESS OF APPLICANT:

B. Braun Medical Inc.
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P.O. Box 19791
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CONTACT PERSON:

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DRUG PRODUCT NAME:

Proprietary:	None
Nonproprietary/USAN:	Cefuroxime and Dextrose in Duplex™ Container
Code Names/#'s:	None
Therapeutic Class:	Cephalosporin, Antimicrobial,

PHARMACOLOGICAL CATEGORY:

Cefuroxime is a cephalosporin with activity against a wide range of gram-positive and gram-negative organisms

DOSAGE FORM:	Solution
STRENGTHS:	750 and 1500 mg
ROUTE OF ADMINISTRATION:	I.V.
DISPENSED:	**_X_ Rx __ OTC**

RELATED DOCUMENTS (if applicable):

DMF: [redacted]

REMARKS/COMMENTS:

This is application provides for the manufacturing and marketing, by B. Braun Medical Inc., of 750 and 1500 mg cefuroxime for injection USP and Dextrose Injection USP in the DUPLEX™

container. The DUPLEX™ container is a patented drug delivery system consisting of a dual chamber, non-PVC plastic container/closure system. The diluent chamber contains 50 mL of the sterile diluent and the drug chamber contains 750 or 1500 mg of the sterile active pharmaceutical ingredient powder, cefuroxime. The DUPLEX™ container is a flexible dual chamber container designed to maintain the integrity of the contents of the drug chamber and diluent chamber during shipping and storage while maintaining them in a ready-to-use configuration without the need for freezing or other special storage conditions. DUPLEX™ container is designed to allow the user to admix the drug and diluent [redacted]

The cefuroxime product insert is in the old format. The original sponsor has not complied with the NDA holders Letter of 1993 and has not submitted information to update the product label. The sponsor of the DUPLEX™ container has not submitted any new data to review and update the microbiology section of the product insert. Due to the circumstances this reviewer will take steps to update the product insert using the information available in the National Committee for Clinical Laboratory Standards documents M7-A5 and M2-A7, The draft Microbiology Guidance Document and the NDA Holders Letter of 1993 as follows.

MICROBIOLOGY:

Cefuroxime [redacted] has in vitro activity against a wide range of gram-positive and gram-negative organis and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericid action of cefuroxime results from inhibition of cell-wall synthesis. Cefuroxime sodium has been shown t active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic and facultative gram-positive microorganisms

Staphylococcus aureus (including penicillinase-producing strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic and facultative gram-negative microorganisms

Enterobacter spp.
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant strains)
Klebsiella spp.
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis

The following *in vitro* data are available, **but their clinical significance is unknown**.
At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefuroxime sodium. However, the safety and effectiveness of cefuroxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic and facultative gram-positive microorganisms

Staphylococcus epidermidis

NOTE: Most strains of *Enterococcus* (e.g., *Enterococcus faecalis*) are resistant to cefuroxime sodium. Methicillin-resistant *Staphylococcus* and *Listeria monocytogenes* are resistant to cefuroxime sodium.

Aerobic and facultative gram-negative microorganisms

Haemophilus parainfluenzae
Moraxella catarrhalis (including ampicillin-and cephalothin-resistant strains)
Proteus mirabilis
Providencia rettgeri

NOTE: Some strains of *Morganella morganii, Enterobacter cloacae,* and *Citrobacter* spp. have been sh by in vitro tests to be resistant to cefuroxime sodium and other cephalosporins. *Pseudomonas* and *Campylobacter* spp., *Acinetobacter calcoaceticus,* and most strains of *Serratia* spp. and *Proteus vulgaris* resistant to most first- and second-generation (including cefuroxime sodium) cephalosporins. For *Salmon* spp. and *Shigella* spp., first and second generation cephalosporins (including cefuroxime sodium) may ap active in vitro but are not effective clinically and should **NOT** be reported as susceptible.

Susceptibility Testing Methods

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1,2] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefuroxime powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* spp.

MIC (µg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

For testing *Haemophilus* spp[a].

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)

8	Intermediate (I)
≥ 16	Resistant (R)

For testing *Neisseria gonorrhoeae*[b]

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

For testing *Streptococcus pneumoniae*[c]

MIC (µg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

Alternatively, isolates of *Streptococcus pneumoniae* could be tested against a 1-µg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible to cefuroxime sodium.

For testing *Streptococcus* spp. other than *S. pneumoniae*

Isolates of *Streptococcus* spp. other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤ 0.12 µg/mL), can be considered susceptible to cefuroxime sodium and need not be tested against cefuroxime sodium.

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM)[2].
[b] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement[2].
[c] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood[2].

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 quality control microorganisms to control the technical aspects of the test procedures. Standard cefuroxime sodium powder should provide the following MIC values:

Microorganism	MIC Range (μg/mL)
Escherichia coli ATCC 25922	2-8
Haemophilus influenzae[d] ATCC 49766	0.25-1
S. aureus ATCC 29213	0.5-2
N. gonorrhoeae[e] ATCC 49226	0.25-1
S. pneumoniae[f] ATCC 49619	0.25-1

[d] This quality control range is applicable to only *H. influenzae* ATCC 49766 tested by a microdilution procedure using HTM[2].

[e] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement[2].

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood[2].

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 [3,4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-μg cefuroxime to test the susceptibility of microorganisms to cefuroxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-μg cefuroxime disk should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* spp.

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

For testing *Haemophilus* spp[g]

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
17-19	Intermediate (I)
≤ 16	Resistant (R)

For testing *Neisseria gonorrhoeae*[h]

Zone Diameter (mm)	Interpretation
≥ 31	Susceptible (S)
26-30	Intermediate (I)
≤ 25	Resistant (R)

For testing *Streptococcus pneumoniae*[i]

Isolates of *Streptococcus pneumoniae* with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible to cefuroxime sodium.

For testing β-hemolytic streptococci only[i]

A β-hemolytic streptococcal isolate that is susceptible to a 10-units penicillin disk (Zone diameter ≥ 28 mm) can be considered susceptible to cefuroxime sodium and need not be tested against cefuroxime sodium.

NOTE: Penicillin disk diffusion test is not reliable with viridans streptococci.

[g] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[4].

[h] These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO_2[4].

[i] This zone diameter standard only applies to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2[4].

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 cefuroxime sodium.

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 cefuroxime disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	20-26
Haemophilus influenzae[j] ATCC 49766	28-36
N. gonorrhoeae[k] ATCC 49226	33-41
S. aureus ATCC 25923	27-35

[j] This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49766 using HTM[4].

[k] This quality control range is only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement[4].

References

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
2. National Committee for Clinical Laboratory Standards. MIC Testing Supplemental Tables NCCLS Document M100- S10 (M7) . NCCLS, Wayne, PA, January 2000.
3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests -Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
4. National Committee for Clinical Laboratory Standards. Disk Diffusion Supplemental Tables NCCLS Document M100- S10 (M2) . NCCLS, Wayne, PA, January 2000. National Committee for Clinical Laboratory Standards. MIC Testing Supplemental Tables NCCLS Document M100- S10 (M7) . NCCLS, Wayne, PA, January 2000.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section of the package insert. These revisions are found on pages 2-7 of this review. The sponsor should be notified of the needed changes in the product insert.

/S/

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Clinical Microbiology Review Officer

Orig. NDA 50,780
HFD-520/Division File
HFD-520/MO/J. Pohlman
HFD-520/Chem/S. Pagay
HFD-520/PharmTox /K. Seethaller
HFD-520/Biopharm TL/F. Pelsor
HFD-520/Micro/S. Altaie
HFD-520/PM/B. Duvall-Miller

Concurrence Only:
HFD-520/DepDir/L Gavrilovich /S/ 11/27/00
HFD-520/TL Micro/AT Sheldon
RD and Final Initialed 11/22/00
/S/ 11/27/00