CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-796

MICROBIOLOGY REVIEW

NDA 50-796
Ceftriaxone for Injection and
Dextrose Injection in the DUPLEX® Container
B Braun Medical Inc

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

NDA 50-796 DATE REVIEW COMPLETED: 31 January 2005

Date Company Submitted: 18 June 2004
Date Received by CDER: 21 June 2004
Date Assigned: 6 July 2004
Reviewer: Connie R. Mahon, MS

NAME AND ADDRESS OF APPLICANT:
B. Braun Medical Inc
2525 McGraw Avenue
PO Box 19791
Irvine CA 92614-5895

CONTACT PERSON:
Richard K. Bourne, PhD
Corporate Vibe President, Regulatory Affairs
Tel No: 949-660-2176
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DRUG PRODUCT NAME:

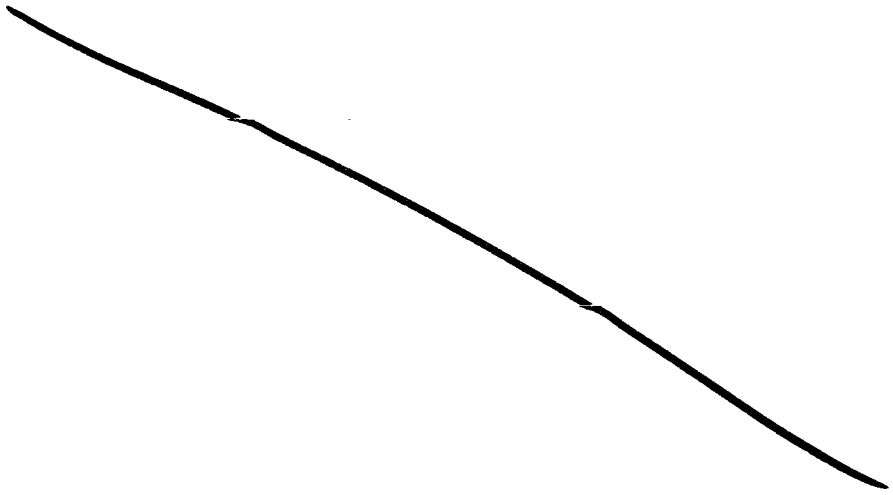
Proprietary Name: Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container
Established Name: Ceftriaxone Sodium

DOSAGE FORM AND ROUTE OF ADMINISTRATION: Ceftriaxone for Injection

DOSAGE AND ADMINISTRATION: Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Drug Delivery System is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 1 g and 2 g ceftriaxone. The diluent chamber contains approximately 50 mL of Dextrose Injection. Dextrose Injection has been adjusted to [redacted] for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

PROPOSED INDICATIONS AND USAGE:

[redacted]



DRUG CATEGORY: Antibacterial, Prescription

PURPOSE OF SUBMISSION:
The sponsor, B. Braun, submits an NDA without clinical data, NDA 50-796, entitled "Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container." B Braun's finished product is based on ROCEPHIN® for Injection, the approved Reference Listed Drug (RLD) for Ceftriaxone injection, marketed by Hoffman La Roche. The labeling will be similar to the REFERENCE LISTED DRUG product, except for inclusion of information on the B. Braun DUPLEX® Container / Closure system.

SUMMARY AND RECOMMENDATION

The Applicant, B. Braun, has submitted a copy of an annotated package insert for review. From the microbiology perspective, this Reviewer finds the Microbiology subsection of the package insert for Ceftriaxone, USP for injection and dextrose injection in the Duplex® container provided by the Applicant acceptable for approval. See Proposed Microbiology section of the Package Insert below. However, the Reviewer recognizes that the nomenclature of certain organisms and the format of the microbiology subsection of the proposed label are not the most current. It is, therefore, recommended that a request be forwarded to the drug innovator to update these sections of the label.

INTRODUCTION

Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container is intended for intravenous use only. It is indicated for the identical intravenous clinical indications as the reference listed drug, ROCEPHIN, (NDA 50-585, approved in 21 December 1984) when

caused by susceptible organisms. In this application, the Applicant 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 50-780 approved 02/21/2001. This application is submitted under 505(b)(2) of the Food, Drug, and Cosmetic Act, and in accordance with the provisions of 21 CFR 314.50 and 314.54. This NDA application is also referenced to the Agency guidelines and memorandum of meeting minutes for the Pre-NDA (PRE IND 67 794) sponsor's meeting with the Division on 13 May 2004. Because the Applicant intends to use the label of the RLD, there is no microbiology data included in this submission. (NDA 50-796 Cover letter).

IN VITRO INFORMATION

Antimicrobial Spectrum of Activity

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

Wenzel RP et al published a cumulative 2000-2001 in vitro antimicrobial activity of expanded-spectrum cephalosporins including ceftriaxone against species of *Enterobacteriaceae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* isolated from hospital patients in four European countries, Canada and the United States. Table 1 shows a summary of the *in vitro* susceptibility tests results of selected gram-negative species isolated from hospital patients with respect to clinical infections. [2] In this study, overall inhibitory activity of Ceftriaxone against most species of *Enterobacteriaceae* was high; *Enterobacter cloacae* and *E. aerogenes* were less susceptible to ceftriaxone than were other Enterobacteriaceae species studied in this report. It showed very limited activity against *Pseudomonas aeruginosa.* For *H. influenzae,* 100 % of isolates from lower respiratory tract infections were susceptible to Ceftriaxone.

Table 1. Ceftriaxone Susceptibilities (% susceptible) of Gram negative Bacteria isolated from hospitalized patients in the United States with respective clinical infections.[2]

Organism	UTI	Bacteremia	SSTI	LRT
E. coli	98.3	98.2	97.8	96
Klebsiella species	94.3	92	93.1	92
Proteus species	99.5	99.7	96	99
Other *Enterobacteriaceae*	77.8			
Serratia spp		91.8	75	89
Citrobacter spp.		80	77.7	75
Enterobacter spp		69.6	71.0	73.7
P. aeruginosa		12.8	13.2	16.0
H. influenzae				100

Additional surveillance data of the susceptibilities of gram negative species to ceftriaxone from the [redacted] Surveillance Database by [redacted][1] are presented on Table 2. The interpretive criteria for susceptibility/resistance were based on the NCCLS interpretive criteria which are the same as those approved by the Agency.

Table 2 *In vitro* Susceptibility Data of other Gram-negative organisms taken from [redacted] Surveillance Database 09/01/2000-09/01/2004[3]

Organism	Number of Isolates	% Susceptible
Acinetobacter baumannii	5457	18
Citrobacter freundii	24876	79.7
Citrobacter koseri	17997	98.4
Enterobacter aerogenes	27189	82.7
Enterobacter cloacae	48632	72
Escherichia coli	816017	98.7
Klebsiella oxytoca	26425	93.6
Klebsiella pneumoniae	178674	96.2
Morganella morganii	18914	93.3
Moraxella catarrhalis	343	99.7
Proteus mirabilis	113431	99.5
Proteus vulgaris	2834	78
Providencia species	62	95.4
Providencia rettgeri	3341	97.7
Serratia marscesens	35744	92
Salmonella species	2761	95.9
Shigella species	305	98.4

For *Neisseria gonorrhoeae* and *N. meningitidis*, 100 % of isolates were susceptible, according to the [redacted] Surveillance Database (1984-2004).[3] I a study published by Karlowsky, et al, ceftriaxone shows activity against strains of penicillin susceptible *S. pneumoniae* (100%) with an MIC_{90} of 0.03 µg/mL (range ≤0.004-0.5 µg/mL), while penicillin-resistant *S. pneumoniae* isolates (92.6%) show an MIC_{90} of 1.0 µg/mL (range 0.12-8 µg/mL).[4] The most recent surveillance data on Table 3 [redacted] show the in vitro activity of Ceftriaxone against gram-positive organisms.

Table 3 *In vitro* Susceptibility Data of Gram-positive organisms taken from [redacted] Surveillance Database 09/01/2000-09/01/2004 [3]

Organism	% Susceptible
Staphylococcus aureus	51.3
Staphylococcus epidermidis	22.8
Streptococcus pneumoniae	91.4
Streptococcus pyogenes	100
Streptococcus agalactiae	100
Viridans streptococci group	90.9

Data in Database (1984-2004) in Table 4 show Ceftriaxone activity against Bacteroides fragilis, Clostridium species, *Peptostreptococcus* species, *Prevotella bivia*, and *Prevotella melaninogenica.*

Organism	% Susceptible
Bacteroides fragilis,	27
Clostridium species	95.6
Peptostreptococcus species	87.8
Prevotella bivia	49.5
Prevotella melaninogenica	70

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. Ceftriaxone shows in *in vitro* tests bactericidal activity that results from inhibition of cell-wall synthesis. [1]

Mechanism(s) of Resistance

The Applicant has provided sufficient information from published articles regarding emerging resistance to Ceftriaxone. (Vol. 1 Section 7 Attachment 1). 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. [5]

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 ceftriaxone. 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. Table 4 below shows susceptibilities to ceftriaxone by species and ESBL gene-type. [6]

Table 4 Susceptibilities to Ceftriaxone by Species and ESBL- gene Types[6]

Species	**No of isolates**	**ESBL gene-type**	**MIC_{50}** (μg/mL)	**MIC_{90}** (μg/mL)
P. mirabilis	127	TEM^+	4	8
P. stuartii	22	TEM^+	4	32
K pneumoniae	32	TEM^+	4	32
	104	SHV^+	8	32
	34	TEM^+ and SHV^+	8	32
	18	Non-TEM/ non-SHV	8	>256
E. coli	11	TEM^+	4	32
	28	SHV^+	4	32
E aerogenes	11	TEM^+	8	16
	14	SHV^+	16	64

The Applicant concludes in the review of the published literature that although resistance to ceftriaxone has been described, in no report was the resistance so high as to render ceftriaxone an inappropriate antimicrobial agent to consider (Vol. 1 Section 7 page 3599).

IN VIVO INFORMATION

Animal studies

The Applicant provided no information regarding animal studies in this submission.

CONCLUSION AND RECOMMENDATIONS

The Applicant, B. Braun, has submitted a copy of an annotated package insert for review. From the microbiology perspective, this Reviewer finds the Microbiology subsection of the package insert for Ceftriaxone, USP for injection and dextrose injection in the Duplex® container provided by the Applicant acceptable for approval. See Proposed Microbiology section of the Package Insert below. However, the Reviewer recognizes that the nomenclature of certain organisms and the format of the microbiology subsection of the proposed label are not the most current. It is, therefore, recommended that a request be forwarded to the drug innovator to update these sections of the label.

REFERENCES:

[1]Yao, J.D., and Moellering, R. Antibacterial agents. A chapter in *Manual of Clinical Microbiology*, 8th ed. Murray, P. et al eds. American Society for Microbiology. Washington DC. 2003. pages 1039-1073

[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]TSN Surveillance Database by Focus Technologies. Accessed 9/01/2004.

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

[5] 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.

[6]Spanu T. et al Occurrence of Extended-spectrumβ-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

PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT

Microbiology

8 Page(s) Withheld

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✓ Draft Labeling

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/s/

Connie Mahon
4/18/05 07:07:22 AM
MICROBIOLOGIST

Frederic Marsik
4/18/05 02:17:16 PM
MICROBIOLOGIST

Lillian Gavrilovich
4/18/05 03:37:41 PM
MEDICAL OFFICER

Product Quality Microbiology Review
Review for HFD-520

29 MAR 2005

NDA:	50-796
Drug Product Name	
Proprietary:	Ceftriaxone for Injection & Dextrose Injection in Duplex Container
Non-proprietary:	
Drug Product Classification:	Anti-infective
Review Number:	1
Subject of this Review	
Submission Date:	June 18, 2004
Receipt Date:	June 21, 2004
Consult Date:	August 3, 2004
Date Assigned for Review:	August 19, 2004
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	N/A
Date(s) of Previous Micro Review(s):	N/A
Applicant/Sponsor	
Name:	B. Braun Medical Inc.
Address:	2525 McGaw Ave Irvine, CA. 92614-5895
Representative:	Susan Olinger
Telephone:	610-390-2722
Name of Reviewer:	John W. Metcalfe, Ph.D.
Conclusion:	Recommended for Approval.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA.

2. **SUBMISSION PROVIDES FOR:** New drug product.

3. **MANUFACTURING SITE:**
The sterile powder API is manufactured at:

[redacted]

The drug product/DUPLEX [redacted] is manufactured at:
B. Braun
Irvine, CA. 926145841

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Powder, For Solution
- Intravenous Injection
- 1g and 2g Ceftriaxone, 50 mL Diluent.

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Anti-infective.

B. **SUPPORTING/RELATED DOCUMENTS:**

[redacted]

C. **REMARKS:**
The submission is an original NDA for a product composed of a powder (Ceftriaxone) packaged in the drug chamber and its diluent (dextrose) packaged as a solution in the second chamber of a plastic container (DUPLEX [redacted]

DMF [redacted] (referenced above) describes the manufacture of the powdered sterile bulk drug, and was reviewed and found to be adequate by this reviewer. DMF [redacted] (referenced above) describes the [redacted] powdered sterile bulk drug at a contract facility: [redacted] This DMF was reviewed during January of 2005 by Dr. Lynne Ensor, OGD review microbiologist, and found to be deficient. A deficiency letter was forwarded to the DMF holder on approximately January 19, 2005. Dr. Ensor reviewed the DMF holder's responses and found them to be adequate in her second review of DMF [redacted] (dated March 23, 2005).

This reviewer placed a phone call to Ms. Susan Olinger (applicant representative) on February 8, 2005 to ask the following questions.

1. This reviewer is unable to find any information in the submission that describes whether or not f[redacted] testing is performed on the [redacted]
   - [redacted]
   - If so, where is it in the submission?
   - What type of test is performed?
2. [redacted]

A response was received back from Ms. Olinger on February 10, 2005 via telephone.

1. The submission contains a reference (page 1783 in the executed batch records) to the [redacted] test that is performed on the [redacted]. In addition, Ms. Olinger will forward the SOP for the [redacted] to the review division as General Correspondence with a desk copy to be sent directly to this reviewer.
2. The requested bacterial endotoxin testing validation raw data will be forwarded as soon as possible.

The written response (dated February 15, 2005) was forwarded to HFD-520 with a desk copy provided to this reviewer. A summary of the information provided follows.

1. [redacted]

2. [redacted]

A phone call was again placed by this reviewer to Ms. Olinger on March 28, 2005 to ask a final question regarding the [redacted]

[redacted]

File name: N050796R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 50-796 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A.

II. Summary of Microbiology Assessments

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

The API is a sterile powder which is manufactured by [redacted] and supplied to the NDA applicant [redacted]. The manufacture of this API is described in DMFs [redacted] (both submitted by [redacted].

The DUPLEX [redacted] (composed of two product compartments) are manufactured by the NDA applicant in Irvine CA, and gamma irradiated at one of two qualified contract facilities [redacted]

The [redacted] are then [redacted] at the NDA applicant's Irvine, CA facility with the sterile API and sterile aqueous dextrose (for reconstitution of the API).

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block
Jim McVey

C. CC Block
In DFS

15 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Microbiology-*2

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/s/

John Metcalfe
3/29/05 03:14:44 PM
MICROBIOLOGIST

James McVey
3/29/05 03:24:37 PM
MICROBIOLOGIST