CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-796

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	50-796
Submission Code	N-000
Letter Date	18-June-2004
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Reviewer Name	Alma C. Davidson
Draft Review Completion Date	28-December-2004
Final Review Completion Date	14-April-2005
Established Name	Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container
(Proposed) Trade Name	CefTRiaxONE sodium for Injection USP and Dextrose Injection USP
Therapeutic Class	4010300
Applicant	B.Braun Medical Inc.
Priority Designation	S
Formulation	Solution, injection
Dosing Regimen	1 to 2 grams once daily
Indication	To treat infections that are proven or strongly suspected to be caused by susceptible bacteria
Intended Population	Adult and Pediatric patients

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EXECUTIVE SUMMARY

Ceftriaxone is a cephalosporin antibiotic marketed as Rocephin®for Injection, the reference listed drug (RLD), by Roche Laboratories Incorporated. Rocephin®(ceftriaxone sodium) for Injection was approved in 1984. This new drug application, NDA 50-796 is for a product by B. Braun Medical Incorporated. The product is Ceftriaxone for Injection and Dextrose Injection in the DUPLEX®Container and is submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A 505(b)(2) application may include results of investigations necessary for approval but were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [21 U.S.C. 355(b)(2)]. These applications are regulated under 21 CFR 314.54 which allow an applicant to rely on the Agency's finding of safety and effectiveness for an approved RLD to the extent such reliance would be permitted under the generic drug approval provisions of section 505(J) of the Act.

NDA 50-796 is submitted to support the use of a new delivery system (Duplex) for ceftriaxone sodium and dextrose in a two-chamber container system. The type of Duplex container in this application utilizes Duplex —container. Other approved products utilizing the Duplex containers are: NDA 50-779, Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container; NDA 50-780, Cefuroxime for Injection USP and Dextrose Injection USP in the Duplex Container; and NDA 50-792, Cefotaxime for Injection USP and Dextrose Injection USP in the Duplex Container. The review of this NDA relies on prior FDA determination of safety and effectiveness for the RLD, Rocephin® for Injection.

1.1 Recommendation on Regulatory Action

The medical reviewer recommends approval for Ceftriaxone for Injection USP and Dextrose Injection USP in the Duplex Container with the proposed changes to the label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no risk management activity recommended at this time.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments at this time.

1.2.3 Other Phase 4 Requests

There are no recommended Phase 4 requests for this application.

1.3 Summary of Clinical Findings

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Ceftriaxone for Injection and Dextrose Injection in the Duplex®Container.

1.3.1 Brief Overview of Clinical Program

This new drug application, NDA 50-796 is for Ceftriaxone for Injection and Dextrose Injection in the DUPLEX®Container by B. Braun Incorporated and is submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This product utilizes a drug delivery system, known as Duplex®container for intravenous administration. This product has similar indications as the RLD, Rocephin®for Injection with the exception of the intramuscular use indication. There are no clinical studies conducted by the applicant.

1.3.2 Efficacy

There are no efficacy data submitted with this application. The efficacy of this product is supported by FDA's finding of efficacy for the RLD, Rocephin® for Injection.

1.3.3 Safety

The safety of this product is supported by FDA's finding of safety for the RLD, Rocephin® for Injection. The reviewer searched the safety profile of the RLD using the data obtained in annual reports and the Adverse Events Reporting System (AERS) database for any additional safety information.

1.3.4 Dosing Regimen and Administration

Ceftriaxone for Injection and Dextrose Injection in the Duplex®Container, 1 g and 2 g is intended only for intravenous use.

1.3.5 Drug-Drug Interactions

There are no drug-drug interactions stated in the label for the RLD. There are no known drug interactions studies conducted by the innovator company (Roche) or by B. Braun.

1.3. 6 Special Populations

Ceftriaxone is excreted via both biliary and renal excretion. There is no adjustment in the dosage of this drug when administered to patients with renal or hepatic impairment. However, in patients with both hepatic and significant renal disease, ceftriaxone dosage should not exceed 2 g daily without close monitoring of serum concentrations.

2 INTRODUCTION AND BACKGROUND

Ceftriaxone has been marketed in the U.S. for over two decades. The NDA for Ceftriaxone (Rocephin® for Injection, NDA 50-585) was approved on December 21, 1984. The drug substance, Ceftriaxone is currently manufactured by Roche AG. The reference listed drug, Rocephin® for Injection is manufactured by Hoffman-La Roche (now Roche) Incorporated. The applicant is seeking approval for Ceftriaxone for Injection and Dextrose Injection in the Duplex® Container for the same indications approved for Rocephin® for Injection with the exception of indications related to intramuscular use.

This NDA is fourth in the series of cephalosporins in the Duplex container submitted by B. Braun. Other approved cephalosporins in the Duplex container include the following:

- NDA 50-779, Cefazolin for Injection USP & Dextrose Injection USP in the Duplex Container - July 27, 2000;

- NDA 50-780, Cefuroxime for Injection USP & Dextrose Injection USP in the Duplex Container - February 21, 2001; and

- NDA 50-792, Cefotaxime for Injection USP & Dextrose Injection USP in the Duplex Container - July 29, 2004.

2.1 Product Information

- Description of the product:

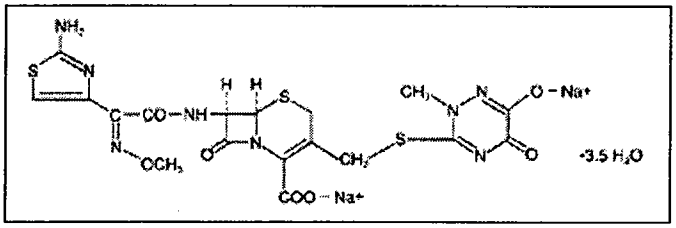
Ceftriaxone for Injection and Dextrose Injection is a sterile, nonpyrogenic, single use, packaged combination of Ceftriaxone sodium and dextrose injection in the Duplex sterile container. The DUPLEX container system is a single-use product that delivers a 1 gram or 2 grams dose of ceftriaxone sodium in 50 mL of dextrose in water. The Duplex container used in this application is the DUPLEX container. The materials used in the DUPLEX container are identical to the materials for the previously approved containers with one exception, the Duplex II container does

The drug chamber contains sterile ceftriaxone sodium and is supplied as a dry powder form equivalent to either 1 g or 2 g of ceftriaxone. The sodium content is approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone. The diluent chamber contains Dextrose in Water for Injection (WFI). The concentrations of Dextrose in WFI are for the 1 g and 2 g doses of the finished Ceftriaxone drug product, respectively. As stated in the proposed package insert, the concentration of hydrous dextrose in water for injection has been adjusted to render the reconstituted drug product iso-osmotic.

Ceftriaxone for Injection USP

Chemical Name: Sodium salt of (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2- methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(*O*-methyloxime), disodium salt, sesquaterhydrate.

Chemical structure:



Chemical formula: $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$

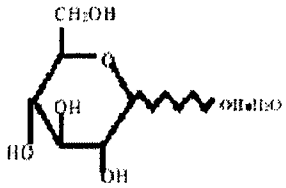
Molecular weight: 661.60

Dosage Strength: 1 g or 2 g

Dextrose USP

Chemical Name: D-glucose monohydrate

Chemical Structure:



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

- Proposed trade name: CefTRiaxONE sodium for Injection USP and Dextrose Injection USP
- Chemical class: Antibiotic
- Pharmacological class: Cephalosporins
- Applicant's proposed indications, dosing regimens, age groups:

The product has the same indications and dosing regimens as the RLD with the exception of the indications related to intramuscular use.

2.2 Currently Available Treatment for Indications

There are numerous antibiotics in the market that are approved for the same indications as Ceftriaxone.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, Ceftriaxone sodium is marketed as Rocephin® for injection and has been available in the U.S. market since 1984. The safety and efficacy profile of ceftriaxone is well-established for several years. There are no new major safety concerns with ceftriaxone at the present time.

2.4 Important Issues With Pharmacologically Related Products

There are no new safety or effectiveness concerns with pharmacologically related products. Recent labeling changes with other cephalosporins included the addition of new text related to requirements of the Final Labeling Rule for Systemic Antibacterial Drug Products Intended for Human Use in accordance with 21 CFR 201.24 and revisions related to "Geriatric Use" statements in the PRECAUTIONS section.

2.5 Presubmission Regulatory Activity

On March 3, 2004, the applicant sent a letter of request for a meeting with the Agency regarding the proposed 505(b) (2) NDA for Ceftriaxone for Injection and Dextrose Injection in the DUPLEX®Container. Subsequently, a face-to-face meeting was held on May 13, 2004 wherein the applicant presented the information package of the proposed NDA submission. A discussion was held between the B. Braun representatives and the

review staff of the Division of Anti-Infective Drug Products (DAIDP) regarding the Duplex [redacted] container delivery system with ceftriaxone.

2.6 Other Relevant Background Information

The applicant does not have any marketing history with ceftriaxone in the Duplex container.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The reader is referred to the CMC review by Dr. Andrew Yu, review chemist for detailed descriptions of the drug product and manufacturing process.

The active drug substance in this product is sterile ceftriaxone sodium USP. The manufacturing facility is [redacted]. The drug product (Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container) manufacturer is B. Braun Medical Inc. located in Irvine, California.

The reader is referred to the Microbiology review by Connie Mahon MS, for microbiology labeling information.

3.2 Animal Pharmacology/Toxicology

There are no new animal pharmacology/toxicology data submitted in this application. Dr. Terry Peters, animal pharmacology/toxicology reviewer stated in her review that the proposed label for Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container is current and acceptable.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The applicant relies on the Agency's finding of safety and effectiveness for the RLD, Rocephin® (ceftriaxone sodium) for Injection.

4.2 Tables of Clinical Studies

There are no clinical studies with this submission.

4.3 Review Strategy

There are no clinical studies conducted by the applicant. The applicant relies on the Agency's finding of safety and effectiveness for the RLD, Rocephin® (ceftriaxone sodium) for Injection. The reviewer reviewed the published literature, annual reports, periodic adverse drug experience report, and FDA Adverse Events Reporting System (AERS) database for additional safety information of ceftriaxone.

4.4 Data Quality and Integrity

There are no audits conducted by the Division of Scientific Investigations (DSI).

4.5 Compliance with Good Clinical Practices

This section is not applicable. There are no clinical trials conducted for this application.

4.6 Financial Disclosures

Since there are no new clinical studies performed by the applicant for this submission, therefore financial disclosure of investigators is not applicable.

5 CLINICAL PHARMACOLOGY

There are no new clinical pharmacology data submitted with this application. Ceftriaxone for Injection and Dextrose injection in the DUPLEX® Container contains the same active ingredient as the RLD, Rocephin® (ceftriaxone sodium) for Injection by Roche. B. Braun Medical Inc. requested a waiver for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence of Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container.

5.1 Pharmacokinetics

The pharmacokinetic data are the same as the RLD, Rocephin® (ceftriaxone sodium) for Injection.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Ceftriaxone for Injection and Dextrose Injection in the Duplex®Container. The review of this NDA relies on prior FDA determination of effectiveness for the reference listed drug.

6.1 Indication

The indications for this product are similar to the RLD, Rocephin® (ceftriaxone sodium) for Injection with the exception of indications related to the use of intramuscular administration.

MO Comment*: All other subheadings (sections) under this heading have been deleted by the reviewer since they do not apply to this review.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant relies on the Agency's finding of safety and effectiveness for the RLD, Rocephin® for Injection in this 505(b)(2) application. In addition, the applicant performed a review of the literature on ceftriaxone safety profile. The reviewer also performed a literature search and reviewed the FDA Adverse Events Reporting System (AERS) on safety information for ceftriaxone.

7.1.1 Deaths

There are no clinical studies conducted by the applicant with this submission. However, there is a fatal adverse event reported in the submitted literature article including hemolytic anemia associated with the use of ceftriaxone. This adverse event is mentioned in the RLD label.

7.1.2 Other Serious Adverse Events

There are no clinical studies conducted by the applicant for this submission. However, there are serious adverse events reported in the literature including hemolytic anemia and anaphylaxis with shock associated with the use of ceftriaxone. These adverse events are mentioned in the RLD label.

7.1.3 Dropouts and Other Significant Adverse Events

This section is not applicable. There are no clinical studies conducted by the applicant for this submission.

***MO Comment**: All other subheadings (sections) under this heading have been deleted by the reviewer since they do not apply to this review.*

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The applicant relies on the Agency's finding of safety for the RLD, Rocephin® for Injection in this 505(b)(2) application.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The Applicant stated that a review of the published literature on ceftriaxone was performed to identify and assess any new clinical safety information. The applicant contends that they reviewed the literature regarding the current validity of microbiological efficacy statements in the labeling. According to the applicant, based on the review of the ceftriaxone literature, there are no changes needed to the currently approved Rocephin®label.

The Office of Drug Safety (ODS) was also consulted to further search the AERS database for safety information on ceftriaxone related adverse events including Jarisch-Herxheimer reaction, nonconvulsive status epilepticus with myoclonus, sore gums, and disulfiram-like reaction. The safety evaluator in ODS, Ronald Wassel found the following results in AERS database: 1) no reports of Jarisch-Herxheimer reaction; 2) 4 cases of status epilepticus of which 2 cases listed ceftriaxone as the primary suspect drug; 3)1 unduplicated case of mycoclonus; 4) 0 report of sore gums; and 5) one case of disulfiram reaction.
(MO Note: The reader is referred to the review by Ronald Wassel, Pharm.D. for further details.)

In the following section, the reviewer has summarized the submitted published literature articles on Ceftriaxone safety including drug interactions and geriatric use information. In addition, the reviewer performed a literature search using PubMed and reviewed the FDA-AERS database and the annual reports for ceftriaxone for additional safety information.

A. This literature review focuses on the safety profile of ceftriaxone. The submitted articles are as follows:

1. Chan DJ, Michelmore HM, Gold J. A diagnosis unmasked by an unusual reaction to ceftriaxone therapy for gonorrheal infection. Med J Aust 2003; 178:404-5.

This is a case report of a 32-year-old HIV positive man who consulted a specialist in an HIV clinic with a complaint of a month's history of rectal discharge. There were no genitourinary symptoms at this visit. Swabs for gonorrheal and chlamydial infection were obtained from the throat, urethra and rectum. His serological tests for syphilis obtained five months earlier were non-reactive. He was referred for serological tests for syphilis one week later. He was given empirical therapy for chlamydia and gonorrhea with a single dose of azithromycin 1 g orally and ceftriaxone 250 mg intramuscularly. The patient had no penicillin allergy. His sexual contacts were apparently unknown. Six hours later, the patient was reported to develop fever, severe chills, rigors, headache, severe myalgia and photophobia. He took paracetamol, which did not relieve his symptoms. However, his symptoms were reported to have spontaneously subsided after 8 hours. On Day 2, the patient noticed a rash on the soles of his feet. Myalgia persisted, but his other systemic symptoms resolved. He contacted the clinic and was told that his acute symptoms suggested a Jarisch-Herxheimer reaction. He was advised to return immediately for syphilis serological tests. *Neisseria gonorrhoeae* was isolated from the rectal culture. The serological tests for syphilis revealed a rapid plasma reagin titer of 1:8 and a reactive *Treponema pallidum* hemagglutination assay. The patient's presentation was consistent with a Jarisch-Herxheimer reaction. This reaction unmasked the secondary syphilis including systemic skin and nodal involvement without a primary chancre. The patient was given 1.5 g procaine penicillin intramuscularly for 14 days. At follow-up, the patient's symptoms resolved completely. His rapid plasma reagin titer decreased to 1:4 after three months and by 6-months, it fell to 1:1.

MO Comment: *The label for Rocephin®(ceftriaxone sodium) does not mention Jarisch-Herxheimer reaction. This reaction has been reported in the literature in association with ceftriaxone use. Bader and Grendelmeier reported a case of a 34-year-old patient who presented with a non-healing skin ulcer on his chest for 8 weeks.[1] The patient had a history of homosexual contacts and his current partner had been treated 10 days previously for acute gonorrhea and infection with Ureaplasma urealyticum. Although this patient was asymptomatic, he was treated with ceftriaxone 250 mg intramuscularly for suspected rectal gonorrhea. A few hours after the injection, the patient developed a skin rash, fever and disorientation. These symptoms resolved ten hours later. A biopsy of the ulcer revealed plasmacellular infiltrate and staining showed multiple spirochetes. Syphilis serology was strongly positive (VDRL test 1:128). Ureaplasma urealyticum was also cultured from the ulcer. Rectal swab was positive for Neisseria gonorrhoeae. Urethral swab and HIV screening were negative. The patient was diagnosed with primary syphilis. The report states that the ulcer began to heal after ceftriaxone treatment. Subsequently, the patient was also treated with benzathine penicillin at 2.4 million units intramuscularly. It was reported that the ulcer healed completely after 8 weeks. Although this reaction is a rare event, this reaction should be added to the label of the RLD, Rocephin® for Injection, in the ADVERSE REACTIONS section.*

2. Grayson ML, McDonald M, Gibson K, et al. Once-daily intravenous cefazolin plus oral probenecid is equivalent to once-daily intravenous ceftriaxone plus oral placebo for the treatment of moderate-to-severe cellulitis in adults. Clin Infect Dis 2002; 34:1440-8.

   This article reports a clinical trial describing a once-daily regimen of cefazolin (2 g intravenously) plus probenecid (1 g by mouth) compared with a once-daily regimen of ceftriaxone (1 g iv) plus oral placebo in a randomized, double-blind equivalence trial of home-based therapy for moderate to severe cellulitis in adults.

   In this trial, adverse reactions were noted in 21 cases (14 in the cefazolin/probenecid arm and 7 in the ceftriaxone/placebo arm). There was one case each of nausea, light-headedness, dizziness, headache and sore gums in the ceftriaxone/placebo arm. According to this report, the overall rates of adverse reactions in the two study groups were similar. However, the patients in the cefazolin/probenecid arm were significantly more likely to complain of nausea and vomiting (11 cases in the cefazolin/probenecid arm versus 3 cases in the ceftriaxone/placebo arm). No other adverse reactions were reported in this study.

   MO Comment*: The adverse reactions noted in this trial including nausea, dizziness and headache are mentioned in the ceftriaxone label. However, the adverse reaction of "sore gums" is not stated in the label.*

3. Martinez-Rodriguez JE, Barriga FJ, Santamaria J, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. Am J Med 2001; 111: 115-9.

   This article reports a series of ten patients with renal failure who developed nonconvulsive status epilepticus in association with cephalosporin therapy. The clinical and electroencephalographic characteristics of these 10 patients who developed alteration of consciousness without convulsions were associated with continuous epileptiform EEG activity while being treated with cephalosporins. Five men and five women with a mean age of 69 ± 14 years developed nonconvulsive status epilepticus while receiving intravenous cephalosporins (ceftriaxone, 2 patients; ceftazidime, 2; and cefepime, 6). Details of the two patients who received ceftriaxone are as follows:

   - A 78 year-old-female with chronic renal failure who received ceftriaxone 2 g/24 h for treatment of meningitis developed drowsiness and myoclonus after 6 days of ceftriaxone therapy. This patient was treated with valproate.

   - An 83 year-old-female with acute renal failure received ceftriaxone 2 g/24 h for treatment of pneumonia and developed drowsiness and myoclonus after 4 days of treatment. She was treated with phenytoin and valproate.

***MO Comment**: Non-convulsive status epilepticus and myoclonus are not stated in the current Rocephin® label. However, seizures are mentioned in the Rocephin® label.*

4. Cornely OA, Bethe U, Seifert H, et al. A randomized monocentric trial in febrile neutropenic patients: ceftriaxone and gentamicin vs cefepime and gentamicin. Ann Hematol 2002; 81:37-43.

   This article describes a prospective, randomized, controlled, single-center trial which evaluated the efficacy and safety of once daily ceftriaxone 2 g plus gentamicin 5 mg/kg in comparison to cefepime 2 g t.i.d. plus gentamicin 5 mg/kg qd in the treatment of febrile neutropenia. Patients with hematological malignancies or solid tumors were assigned to ceftriaxone or cefepime, along with gentamicin. Two hundred eleven episodes were included. Nausea/vomiting and diarrhea occurred in 7 (6.5%) and 13 (12.1%) cases in the ceftriaxone-gentamicin group, respectively; and in 17 (17%) and 5 (5%) patients in the cefepime-gentamicin group. A report of an allergic grade-1 rash and an intense grade-2 pruritus reversed to normal after cessation of ceftriaxone. Creatinine levels above the upper limit of normal were observed in 9 (8.4%) cases in the ceftriaxone-gentamicin arm and in 4 (4%) in the cefepime-gentamicin arm.

   ***MO Comment**: The adverse reactions noted in this trial including nausea, vomiting, diarrhea, rash and pruritus are mentioned in the Rocephin® (ceftriaxone) label.*

5. Cornely OA, Bethe U, Salzberger B, et al. Randomized controlled monocentric comparison of once daily ceftriaxone with tobramycin and cefotaxime three times daily with tobramycin in neutropenic fever. Ann Hematol 2001; 80: 103-8.

   This article describes a prospective, randomized, controlled, single center trial which evaluated the efficacy and safety of once daily ceftriaxone 2 g plus tobramycin 5 mg/kg in comparison to cefotaxime 2 g tid plus tobramycin 5 mg/kg qd in the treatment of neutropenic fever. There were 114 patients with 160 episodes. The study states that in 10 episodes, adverse reactions were observed that might be attributed to the study medication. These reactions were allergic skin reactions (2), nausea (3), and diarrhea (2) in the ceftriaxone/tobramycin arm. In the cefotaxime/tobramycin arm, there were 2 reports of allergies, 2 nausea, and 1 diarrhea. No other adverse reactions were reported in this study.

   ***MO Comment**: The adverse reactions noted in this trial including nausea and diarrhea are mentioned in the Rocephin® (ceftriaxone) label. Allergic skin reactions per se are not stated in the label for Rocephin®; however, rash and pruritus are mentioned under the "Hypersensitivity" heading in the ADVERSE REACTIONS section.*

6. Ernst MR, van Dijken PJ, Kabel PJ, Draisma JM. Anaphylaxis after first exposure to ceftriaxone. Acta Paediatr 2002; 91:355-6.

   This is a case report of a 3-year-old boy who presented with high fever and petechial rash over his trunk and extremities. There were no signs of meningeal irritation. After blood cultures and laboratory testing were taken, ceftriaxone was administered intravenously at a dose of 100 mg/kg. Within few minutes of receiving ceftriaxone, the patient developed anaphylaxis with shock. Epinephrine, clemastine fumarate, dexamethasone, and fluids were administered. The report states that the patient was intubated and managed further in the intensive care unit. Chloramphenicol was given at a dose of 50 mg/kg intravenously for 7 days without any reactions observed. The patient was apparently discharged in good clinical condition. After a month, this reaction was confirmed by an in vivo controlled challenge test after a negative skin testing and ceftriaxone-specific IgE.

   ***MO Comment**: Anaphylaxis is stated in the Rocephin® (ceftriaxone sodium) label.*

7. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme Disease (STOP-LD): a randomized double masked clinical trial. Neurology 2003 Jun 24; 60(12):1923-30.

   This article describes a single center, randomized double-masked placebo-controlled trial in 55 patients with Lyme disease. These patients were recruited between January 1997 and July 1999 in Suffolk County, Long Island. These patients were to have persistent severe fatigue for at least six or more months after standard antibiotic therapy for Lyme disease. Eligible patients were randomized to receive 28 days of IV ceftriaxone 2 g/d or IV placebo. Diarrhea occurred more often in the ceftriaxone group (43% versus 25%). Four life-threatening adverse events occurred in the study: One case of anaphylaxis in the ceftriaxone group and three cases of sepsis in the placebo group. The article states that these patients were hospitalized and recovered within 24 hours of admission without sequelae at one and six months. Discontinuation of treatment prematurely occurred in patients who developed infected IV lines and two patients with minor allergic reactions in the ceftriaxone group.

   ***MO Comment**: Diarrhea and anaphylaxis are stated in the Rocephin® label. The mentioned minor allergic reactions were not described in the article above.*

8. Lamb HM, Ormrod D, Scott LJ, Figgitt DP. Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. Drugs 2002;62:1041-89.
   This review article on ceftriaxone describes its antibacterial activity, mechanisms of resistance, effects on intestinal flora, pharmacodynamics, pharmacokinetics, therapeutic use in community-acquired and nosocomial infections, and tolerability. The safety profile of ceftriaxone is described including gastrointestinal adverse events, other systemic events, local injection site reactions, and laboratory changes.

***MO Comment**: All the adverse events described in this update are stated in the Rocephin® label.*

9. Seltsam A, Salama A. Ceftriaxone-induced immune hemolysis: two case reports and a concise review of the literature. Intensive Care Med 2000; 26: 1390-4.

   This report describes two cases of ceftriaxone-induced immune hemolytic anemia. The first patient was a 68-year-old woman admitted to the hospital because of sciatica. She developed paraparesis a few days later. A diagnosis of meningoradiculitis was then made and she was treated with antituberculous drugs and ceftriaxone. After 10 days of treatment with ceftriaxone, the patient complained of lumbar pain. Her hemoglobin level dropped to 7.2 g/dL due to a massive hemolytic reaction with hemoglobinuria. Her serum lactate dehydrogenase was 8600 U/L; and total bilirubin was 15.2 mg/dL. Despite the administration of several units of blood, her hemolysis increased and renal failure developed. Ceftriaxone was discontinued since drug-induced immune hemolytic anemia was suspected. Her renal function recovered after 5 days of dialysis. The report states that her neurological symptoms gradually improved.

   The second patient was a 64-year-old woman with obstructive jaundice due to carcinoma of the bile duct. She was admitted to the hospital for treatment. Ceftriaxone was administered for antibiotic prophylaxis during her several endoscopic retrograde cholangiopancreatography (ERCP) procedures. This procedure with stent insertion in the bile duct and percutaneous transhepatic drainage was done eight times. The report states that prior to the last scheduled drain change, the patient received 2 g of ceftriaxone intravenously. Half an hour later, she developed lumbar pain and shock. Laboratory findings showed hemoglobin of 5.0 g/dL, LDH increased to 20,000 U/L, and hemoglobinuria. The report states that the patient died later on despite all therapeutic measures.

   ***MO Comment**: Hemolytic anemia is stated in the Rocephin® label. This reaction is very serious with a potentially fatal outcome.*

B. This review concerns the drug interactions information of ceftriaxone. The literature articles are summarized as follows:

1. Moskovitz BL. Clinical adverse effects during ceftriaxone therapy. Am J Med 1984; 77:84-8.

   This report summarizes the clinical adverse effects of ceftriaxone reported in 153 individual studies. The safety of ceftriaxone administered parenterally at various doses for time periods ranging from a single injection to up to 6 weeks was evaluated in 2, 640 patients. The incidence of adverse effects (n=215 patients) was as follows: gastrointestinal (3.45%); hypersensitivity (2.77%); local reactions at the site of injection or infusion (1.86%); central nervous system reactions (0.27%), candidal overgrowth (0.23%), and various miscellaneous

reactions (0.42%). The incidence of gastrointestinal and hypersensitivity adverse reactions in the pediatric population was 5.63% and 3.3%, respectively. When ceftriaxone was administered twice daily, there was a statistically significant increase in local reactions. One notable adverse effect, a disulfiram-like reaction was reported in one patient who received ceftriaxone followed by intake of alcoholic beverage. This patient apparently rechallenged himself two days later with three glasses of wine and experienced a similar reaction.

***MO Comment**: Disulfiram-like reaction with alcohol after ceftriaxone use is not mentioned in the RLD, Rocephin® for Injection label. There is one report in the literature regarding disulfiram-like reaction associated with ceftriaxone use and alcohol intake.[2] This reaction has also been reported in patients who received cefamandole, moxalactam or cefoperazone, notably cephalosporins containing the methyltetrathiozolethiol (MTT) side-chain at the 3-position of the nucleus.[3]*

2. Fekety FR. Safety of parenteral third-generation cephalosporins. Am J Med 1990; 88:38S-44S.

   This review describes the safety profile of the third-generation cephalosporins including cefotaxime, ceftizoxime, ceftriaxone, moxalactam, cefoperazone, and ceftazidime. The side effects associated with the different cephalosporins discussed in this article included coagulopathies and bleeding, antibiotic-induced hypoprothrombinemia, hypersensitivity reactions, immune-mediated hematologic reactions, gastrointestinal, hepatic and biliary reactions, superinfections, nephrotoxicity, neurotoxicity, and disulfiram-like reactions.

   ***MO Comment**: The above reactions are mentioned in the ceftriaxone label except the disulfiram-like reactions. Disulfiram-like reaction is mentioned in the label of cephalosporins containing the methyltetrathiozolethiol (MTT) side- chain moiety.*

3. Dasgupta A, Dennen DA, Dean R, McLawhon RW. Displacement of phenytoin from serum protein carriers by antibiotics: studies with ceftriaxone, nafcillin, and sulfamethoxazole. Clin Chem. 1991 Jan; 37(1):98-100.

   This article reports the studies on in vivo and in vitro displacement of phenytoin by ceftriaxone, nafcillin, and sulfamethoxazole. For the in vitro test, serum from patients who received phenytoin without other concurrent medications were combined to create two serum pools with albumin concentrations of 25 and 32 g/L. The third serum pool with albumin concentration of 45 g/L came from healthy volunteers. Microliter quantities of ceftriaxone or nafcillin were added to 1 mL aliquots from the 3 serum pools to mimic peak therapeutic concentrations of each drug in the serum. Concentration of free phenytoin was measured in the protein-free ultrafiltrates by fluorescence polarization immunoassay. The total concentrations of phenytoin were also measured by this technique. Table 1 demonstrates the in vitro results for ceftriaxone: (Note: The reviewer included only the results for ceftriaxone.)

   Table 1. In vitro displacement of Phenytoin by Ceftriaxone

Albumin g/L	n*	Free phenytoin, μmol/L		
		Control	Ceftriaxone, μmol/L 270	361
25	3	8.12 (0.28)	9.39 (0.12)	9.93 (0.36)
32	3	9.74 (0.24)	10.61 (0.04)	11.20 (0.24)
45	4	6.01 (0.08)	6.65 (0.12)	6.81(0.12)

*Number of replicates per run.

The in vitro study showed displacement of free phenytoin from protein-binding sites by ceftriaxone at both ceftriaxone concentrations.

For the in vivo study, concentrations of free phenytoin were monitored in patients receiving ceftriaxone, nafcillin, or sulfamethoxazole. The article states that the data of free phenytoin concentration prior to antibiotic administration were not available, but the authors observed a decrease in the concentration of free phenytoin when nafcillin was discontinued. Concentrations of albumin in the serum of the patients remained unchanged. The authors stated that the concentration of free phenytoin calculated by their equation is less than the measured concentrations of free phenytoin. According to the authors this discrepancy suggests the in vivo displacement of phenytoin from protein carriers by these antibiotics. (See Table 2).

Table 2. Increased concentration of Free Phenytoin by concurrent administration of antibiotics in vivo

Displacing drug *	Albumin g/L	Total phenytoin, µmol/L	Free phenytoin, µmol/L	
			Calculated	Measured
Ceftriaxone	**34**	**24.2**	**3.4**	**4.0**
Nafcillin	34	32.1	4.7	6.5
	45	50.3	5.7	8.4
	46	68.5	7.7	9.3
	42	29.3	3.4	3.9
Bactrim	39	27.3	3.4	4.8
	33	60.6	9.6	11.5
	32	31.7	5.0	7.5
	32	36.0	5.7	6.9
	36	20.6	2.7	3.1

*An in vivo concentration of the antibiotics was not obtained.

The authors concluded that these antibiotics could displace phenytoin from protein-binding sites in vivo and in vitro. Since this displacement effect is modulated by the measured albumin concentration, therefore it is necessary to monitor free phenytoin in hypoalbuminemic patients concomitantly receiving these antibiotics to reduce the risk of phenytoin toxicity.

MO Comment: *This interaction merits mentioning in the ceftriaxone label specifically in a "Drug Interactions" subsection. The reviewer agrees with the authors the importance of monitoring free phenytoin in hypoalbuminemic patients concomitantly receiving ceftriaxone to monitor potential risk of phenytoin toxicity. The Rocephin® label does not have this subsection.*

4. Mimoz O, Soreda S, Padoin C, et al. Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: a model to explore the effects of decreased protein binding capacity on highly bound drugs. Anesthesiology 2000; 93:735-43.

This article describes the study conducted in Bicêtre Hospital-surgical intensive care unit, France. This study was designed to determine the pharmacokinetics and pharmacodynamics

of ceftriaxone after administration to previously healthy postsurgical patients with iatrogenic hydroxyethyl starch-induced hypoalbuminemia. Eleven patients (6 men and 5 women) and 11 volunteers were studied. Eleven hypoalbuminemic (serum albumin <25 g/L) patients with age (±5 yr), sex, body surface area (±10%) matched with the healthy volunteers received ceftriaxone 2 g dose infused over 15-minutes. The pharmacokinetic parameters derived from total ceftriaxone concentrations were similar for the two groups, except for the median corrected volume of distribution at steady state, which was increased to 0.18 L/kg in patients, compared with 0.15 L/kg in volunteers. AUC time curve was twice as high in patients as in volunteers (median 192, range 114-301 vs median 122, range 84-169). The free ceftriaxone concentration remained more than 4 mg/L in patients. The authors concluded that patients with iatrogenic hypoalbuminemia compared with healthy volunteers have higher free ceftriaxone concentration during the 24 hr after its administration. This increases the drug distribution into the extravascular space and may enhance effectiveness.

MO Comment: *This study shows that iatrogenic hydroxyethyl starch-induced hypoalbuminemia produces higher free ceftriaxone concentration in plasma. This effect could potentially lead to increase in adverse effects. This drug interaction is not mentioned in the Ceftriaxone label.*

5. Vomiero G, Carpenter B, Robb I, Filler G. Combination of ceftriaxone and acyclovir-an underestimated nephrotoxic potential? Pediatr Nephrol 2002; 17:633-7

This article describes a retrospective review of 17 patients (age range 1-14 years) over a 6-month period who were treated with combination therapy of ceftriaxone and acyclovir for suspected meningoencephalitis. Mean acyclovir and ceftriaxone doses were 1,222±304 and 2,315±509 mg/m^2 per day, respectively. Three patients developed acute renal failure with a peak creatinine of up to 865% above baseline, which occurred 2-3 days after starting combination therapy. The authors defined increased in serum creatinine as a rise above baseline creatinine. The rise was calculated by using the proportion of the highest serum creatinine on the combination therapy divided by the serum creatinine on admission. The renal failure of these patients showed a tubular proteinuria pattern. Renal biopsy of one patient showed a tubulotoxic picture without evidence of crystals. In 12 of 17 patients (70%) there was a significant increase in serum creatinine. The report states that this incidence of renal impairment is significantly greater than the literature report (16%) with acyclovir alone. The authors stated that the degree of renal impairment in their patients correlated significantly with the acyclovir dose and no correlation was found with the ceftriaxone dose. The authors concluded that the addition of a second nephrotoxic drug aggravated the extent of renal injury in these patients. The mechanism of renal injury was tubulotoxicity. The authors stated that caution should be exercised when using this potentially nephrotoxic combination with close monitoring of serum creatinine.

MO Comment: *The potentially nephrotoxic combination of ceftriaxone and acyclovir should be mentioned in the Ceftriaxone label.*

6. Ali BH. Agents ameliorating or augmenting experimental gentamicin nephrotoxicity: some recent research. Food Chem Toxicol. 2003 Nov; 41(11):1447-52.

   This article reviews some of the literature on the effects of drugs that ameliorate or augment gentamicin nephrotoxicity. It reports that co-administration of certain antibiotics has been shown to reduce the nephrotoxicity of several aminoglycosides. Beauchamp et al have reported that ceftriaxone (100 mg/kg every 12 h, s.c. for 4 or 10 days) protects the Sprague-Dawley rats against the biochemical and histological signs of tobramycin nephrotoxicity. These investigators contend that cephalosporin significantly reduced the renal intracortical accumulation of tobramycin.

   MO Comment*: A protective effect of ceftriaxone against the nephrotoxicity of tobramycin in rats has been cited in this paper.*

7. Kishore K, Raina A, Misra V. Jonas E. Acute verapamil toxicity in a patient with chronic toxicity: Possible interaction with ceftriaxone and clindamycin. Ann Pharmacother 1993; 27:877-80. Comment in: Ann Pharmacother 1993; 27:1544-5.

   This article reports a case of acute toxicity in a patient with chronic verapamil toxicity, possibly precipitated by intravenous administration of highly protein-bound drugs, ceftriaxone and clindamycin. This is a case of a 59-year-old man who had been receiving verapamil (sustained-release) 240 mg every 12 hours for more than two years for hypertension and phenytoin 300 mg/d for many years for prophylaxis against seizures. He had a history of thrombotic cerebrovascular accident, right hip fracture with prosthetic replacement, chronic alcoholism, and diabetes mellitus. The patient presented to the emergency hospital with a two-day history of cough and shortness of breath associated with nausea, vomiting and cyanosis. A junctional rhythm was noted at presentation. The patient was diagnosed with pneumonia and ceftriaxone 1g q 24 hr and clindamycin 900 mg q 8 hr intravenously were administered. This administration was followed by acute verapamil toxicity with complete heart block requiring cardiopulmonary resuscitation and insertion of a temporary pacemaker. The report states that verapamil concentration obtained approximately 12 hours after the patient's arrival to the hospital and 20 hours after the last dose was 212 ng/mL (normal range at steady-state was 125-400 ng/mL). Apparently the patient spontaneously reverted to normal sinus rhythm after 16 hours. All his cardiac evaluations were reported as normal. The authors stated that in view of the patient's subsequent conversion to normal sinus rhythm and normal cardiac studies, the junctional rhythm seen on admission attributable to chronic verapamil toxicity cannot be excluded. The authors concluded that the administration of ceftriaxone, clindamycin or both agents might have precipitated the acute verapamil toxicity by displacing verapamil from its protein-binding sites, leading to sudden increase in free verapamil concentration. The authors

emphasized that extreme caution is necessary when a highly protein-bound drug is administered to a patient receiving verapamil in order to avoid serious cardiovascular adverse effects.

MO Comment: *Displacement reactions following the use of two highly protein-bound drugs (ceftriaxone and clindamycin), competing with verapamil for the same binding sites should be stated in the Drug Interaction subsection of the ceftriaxone label. The RLD, Rocephin® for Injection label does not contain a "Drug Interactions" section. This reaction could potentially lead to serious cardiovascular adverse effects in certain patients.*

C. This literature review concerns information on use of ceftriaxone in geriatric patients. The articles are summarized as follows:

1. Giamarellou HJ, Tsagarakis J, Petrikkos G, et al. Ceftriaxone: therapeutic results in various infections and kinetic studies. Arzneimittelforschung 1984; 34:321-5.

   This study reports the clinical studies including pharmacokinetics of ceftriaxone in 67 patients with different bacterial infections. There were elderly patients, up to the age of 83 years in these studies but the exact number of patients greater than 65 years of age was not specified in this article. The adverse reactions were reported as minor including mainly local pain at the site of injection. In nine patients ceftriaxone produced local infiltration in subcutaneous tissue; and one patient developed a sterile abscess in the buttock. There were no age-related differences in toxicity or pharmacokinetics discussed in this article.

2. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. Clin Pharmacokinet 2001;40: 685-84.

   This article discusses the effect of age on ceftriaxone kinetics. The pharmacokinetic-pharmacodynamic parameters for ceftriaxone based on free concentrations were studied in eight healthy elderly patients at doses of 1 g intravenously. On the basis of ceftriaxone's half-life, the authors concluded that no dosage adjustments are needed in the geriatric population, except in the presence of malnutrition or marked renal impairment. The free AUC's in the geriatric patients were disproportionately higher than in the younger individuals because of the effects of aging on plasma protein binding and the effect of reduced creatinine clearance in the elderly, lowering the ability to excrete the free drug.

   MO Comment: *These two papers did not mention the specific number of geriatric patients (≥ 65 years of age) involved in the studies. In the first study, the adverse effects were reported but were not specified in what age population they occurred. In the second study, there is no mention of the specific age of the elderly patients and no report of adverse effects. Therefore,*

the information that these papers provided is insufficient to support the applicant's proposed statements in the Geriatric Use subsection.

D. The following references support the dextrose contraindication in the Ceftriaxone label:

1. Randolph TG, Rollins JP, Walter CK. Allergic reactions following the intravenous injection of corn sugar (Dextrose). Archives Surgery 1950; 554-564.

This paper describes five case reports of corn sugar (dextrose) sensitivity as follows:

Case #1: A 22-year-old woman who has a prior history of intermittent asthma since childhood, acute GI upsets at age 15, perennial allergic rhinitis and chronic fatigue at age 19. In the months of July and August for the preceding two years, she also developed chronic colds accompanied by daily elevations of temperature and tender swollen cervical glands. Her reactions were not associated with high pollen or fungus counts or explained on the basis of infectious mononucleosis or other causes. However, the report states that her food diary revealed that she developed sneezing, pruritus and urticaria following meals containing corn on the cob. A food test with corn was followed by abdominal cramps, generalized itching, marked fatigue, and recurrence of tender, swollen anterior cervical glands. The report states that a complete elimination of corn products and continuation of dust therapy afforded complete relief of symptoms. A test was performed in which the patient ingested USP dextrose, and the patient developed acute reactive symptoms. Two years later, the patient received 25 cubic centimeters of 5% dextrose intravenously and 12 minutes later she developed severe headache with pain and tenderness of the mastoid area bilaterally, generalized aching of her extremities, and fatigue which persisted for two days. Four days later after being symptom free, she underwent another rechallenge test of intravenous injection of 20 cc. of 50% dextrose, which again led her to develop acute allergic myalgia with marked stiffness of her neck and back.

Case #2: A 30-year-old female dietitian who has a history of constant headache, posterior cervical myalgia, generalized aching for three years. She also has a history of episodic nausea, vomiting, and diarrhea for eight years. Her history of hypersensitivity to administration of corn syrup was first noted when she was hospitalized for nausea of pregnancy and irritable colon. The patient received three intravenous injections of 5% dextrose in sodium chloride solution on successive days. Two hours after the third injection, she complained of chills with pain on right side of her chest and midback; at three hours, an increase in nausea and diarrhea developed; and 3 ½ hours later, she developed severe chills and a fever of 100.4°F. Seven hours later, her temperature rose to 102°F and she developed severe abdominal cramps. She recovered after two days without receiving any further intravenous dextrose solution. These acute reactions were repeated during several hospitalizations and receiving dextrose solutions intravenously. A corn sugar test was

performed and revealed similar acute reactive symptoms, while an isotonic sodium chloride solution test failed to develop such reactions.

Case #3: This is a 54-year-old housewife with a history of intermittent headaches for 15 years. Over the next decade, her headaches became constant and were associated with dizziness. She also complained of weakness, alternating constipation and diarrhea, and chronic dermatitis in her hands. A food test showed that she was allergic to a wide variety of foods. Corn gave her the most reactions. Her sensitivity to corn persisted to such a degree that even ingestion of small amount of corn contained as excipients in pharmaceutical tablets and ingestion of dextrose encountered by accident in commercially prepared foods caused symptoms. She received intravenous injection of 5% dextrose as previously described for other cases. Few minutes later, she developed drowsiness, muscle pain over her neck and extremities, sniffling, coughing, lacrimation, headache and generalized fatigue. Her symptoms gradually tapered off during the following two days.

Case #4: A 37-year-old woman who has a chronic history of perennial nasal allergy with intermittent nasal obstruction and other acute exacerbation of symptoms such as sore throat and enlargement of anterior cervical glands. She underwent a food test and was found to be sensitive to wheat, corn, rye, milk, eggs and pork. Upon avoidance of all sources of corn, the patient reported an improvement for the first time in many months. After a second feeding test with corn meal gruel and corn sugar, she developed severe chills and headache. Two months later, she underwent the test of 25 cc. of 5% dextrose injection intravenously; seven hours later, she developed angioedema of the face but was otherwise stable and was reported as unusually tired and depressed. Ten days later, she was given another test of 500 cc. of 5% dextrose intravenously. Minutes later, she developed mild to severe frontal headache, neck and upper back pain, nasal congestion, belching, and excessive gas. Her severe fatigue, drowsiness, decreased mental acuity, and neck and back pain persisted until the following day. She apparently recovered after a day.

Case #5: A 41-year-old male engineer who has a two-year history of recurrent headaches and rhinitis. The patient's symptoms included a right frontal area pressure sensation, scotomas, inability to focus his eyes, neck pain, fatigue, nausea and diarrhea. The report states that his physical examination showed no significant abnormalities. On allergy testing, he reacted to house dust on cutaneous testing. Individual food tests revealed corn sensitivity. With dust therapy and avoidance of corn, the patient reported a complete relief of his symptoms for several weeks. He then underwent the intravenous 5% dextrose test and few minutes later, he developed warm sensation and flushing of his face. After ten minutes, he developed chills and rigors and twenty minutes later, he developed headache, neck pain, and throat secretions.

2. Randolph TG, Rollins JP, Walter CK. Allergic reactions following the intravenous injection of corn sugar (Dextrose or Glucose). *J. Lab & Clin Med* 1949; 34:1741.

This abstract reiterates the four case reports of patients with corn sensitivity. In each case the diagnosis of corn sensitivity was made as a result of the experimental feeding of corn meal gruel and corn sugar after four days of complete corn avoidance. Intravenous administration of 25 cc of 5% dextrose resulted in severe symptoms which were clinically similar to those observed following the ingestion of corn meal and corn sugar.

***MO Comment**: It is not stated in this abstract whether these four cases are the same cases previously described by Randolph et al in article (#1).*

3. Sandberg DH. Persistent vomiting due to sensitivity to corn sugar or dextrose present in intravenous fluids. *Pediatric Research* 1977; 11(4): 449(#466).

This is a case report of a 13-year-old white female admitted to the University of Miami Medical Center because of persistent vomiting with weight loss for two months. She also complained of chronic persistent abdominal pain. An exploratory surgery with appendectomy revealed no apparent abnormality. The patient developed nausea and vomiting after all oral intake postoperatively. A cineesophagogram and endoscopy revealed minimal esophagitis and pylorospasm. Her vomiting persisted while on intravenous fluids. The patient was given intragastric drip feedings of Sustacal R with temporary improvement of her symptoms. Intragastric milk was tolerated except for corn products. An intradermal provocative food testing with corn extract produced symptoms suggesting corn sensitivity. Intravenous administration of 25 ml 5% dextrose with water reproduced all her previous GI symptoms. A corn meal and corn syrup produced nausea and vomiting. Laboratory results including C3 was low with elevated serum IgE and IgM. The patient gained weight in 3 weeks after avoiding corn products and had no recurrence of her GI symptoms.

***MO Comment**: All other subheadings (sections) under this heading have been deleted by the reviewer since they do not apply to this review.*

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container, 1 g and 2 g is intended for intravenous use only.

8.2 Drug-Drug Interactions

There are no drug-drug interactions studies conducted for this application. *(MO Note: The reader is referred to Section 7.2.2 in this review [literature review, B] for summary of literature articles on drug interactions.)*

8.3 Special Populations

The indications for use of this product are similar to the RLD except for the indication relating to intramuscular use. There is no special dosing for patients with hepatic or renal insufficiency.

8.4 Pediatrics

There are no pediatric studies conducted by the applicant for this application.

8.5 Advisory Committee Meeting

There is no advisory committee meeting for this submission.

8.6 Literature Review

The reviewer performed additional literature search for ceftriaxone safety profile. There is no new safety issue for ceftriaxone besides the information obtained from the published articles submitted by the applicant.

8.7 Postmarketing Risk Management Plan

There are no postmarketing risk management plans stated by the applicant.

8.8 Other Relevant Materials

There are no other relevant review materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA 50-796, for the DUPLEX Container with Ceftriaxone for Injection and Dextrose Injection is fourth in a series of cephalosporin products developed by B. Braun Medical Inc. These series of products have been submitted in accordance with Section 505 (b)(2) of the Food, Drug, and Cosmetic Act, as regulated under 21 CFR 314.54. The recommendation for approval

of this application is based upon FDA prior finding of safety and effectiveness for the RLD, Rocephin® for Injection.

9.2 Recommendation on Regulatory Action

The medical reviewer recommends approval for Ceftriaxone for Injection USP and Dextrose Injection USP in the Duplex Container with the proposed changes to the label.

9.3 Recommendation on Postmarketing Actions

There is no recommendation on postmarketing actions at this time.

9.4 Labeling Review

The applicant made the following labeling changes to the Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container:

- Deletion of all the text relating to intramuscular use
- Addition of a statement in the PRECAUTIONS/Pediatric Use subsection and DOSAGE AND ADMINISTRATION (Pediatric Patients) section
- Addition of antibiotic resistance statements in accordance with 21 CFR 201.24
- Replacement of reference listed drug's specific information and format with B. Braun's information and product name
- Addition of information pertaining to dextrose
- Addition of new information pertaining to the container/closure system (i.e., Duplex container is Latex-free, PVC-free, and DEHP-free.)

(MO Note: The reader is referred to Appendix 10.2 for a line-by-line review of the label.)

33 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

11 REFERENCES

1. Bader U, Schmid-Grendelmeier P. Atypical manifestation of primary syphilis. Am J Med 2000 Apr; 108:521-522.

2. Bilstein SA, Sudol TE. Disulfiram-like reactions rare with ceftriaxone. Geriatrics. 1992 Apr; 47(4):70.

3. Uri JV, Parks DB. Disulfiram-like reaction to certain cephalosporins. Ther Drug Monit. 1983 Jun; 5 (2): 219-24.

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