

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
050823Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 50-823 |
| Priority or Standard | Standard |
| Submit Date(s) | August 12, 2010 |
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| PDUFA Goal Date | June 13, 2011 |
| Division / Office | DAIOP/OAP |
| Reviewer Name(s) | Alma C. Davidson, M.D. |
| Review Completion Date | April 11, 2011 |
| Established Name | Ceftazidime for Injection and Dextrose Injection in Duplex Container |
| (Proposed) Trade Name | Ceftazidime for Injection, USP and Dextrose Injection, USP in Duplex [®] Container |
| Therapeutic Class | Cephalosporin |
| Applicant | B. Braun Medical, Inc. |
| Formulation(s) | Solution, injection |
| Dosing Regimen | 1 to 2 grams every 8h or 12h |
| Indication(s) | To treat infections that are proven or strongly suspected to be caused by susceptible bacteria |
| Intended Population(s) | Adult (b) (4) patients |

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1 Recommendations/Risk Benefit Assessment

The Applicant, B. Braun Inc., has submitted this 505(b)(2) new drug application (NDA) for Ceftazidime for Injection, USP and Dextrose Injection, USP in the Duplex[®] Container using the GlaxoSmithKline (GSK) product, FORTAZ[®] in Add Vantage[®] 1 g and 2 g vials, as the reference listed drug (RLD). There are no clinical trials conducted by the Applicant to support this 505(b)(2) NDA for Ceftazidime for Injection and Dextrose Injection in the Duplex[®] Container. The review for this NDA relies on the prior FDA determination of effectiveness and safety of ceftazidime based on studies which were not conducted by or for the Applicant. The Applicant provided a safety update for ceftazidime by including a review of recently published literature.

1.1 Recommendation on Regulatory Action

Based on the review of the safety update for ceftazidime injection, the reviewer finds no new information that could impact the safety of ceftazidime. From a clinical standpoint, this application is recommended for approval. The overall approval of this application is contingent upon the adequacy of the chemistry, manufacturing, and controls (CMC) review. The approval of Ceftazidime for Injection, USP and Dextrose Injection in the Duplex[®] Container final label in Physician's Labeling Rule (PLR) format is pending review by all disciplines.

1.2 Risk Benefit Assessment

Not applicable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

Ceftazidime is a semi-synthetic, broad spectrum third generation cephalosporin antibacterial agent. It has enhanced activity *in vitro* against Gram-positive and Gram-negative bacteria. Ceftazidime has been marketed in the U.S. for over two decades. The NDA for the reference listed drug (RLD), FORTAZ[®] for Injection, NDA 50-578, was initially approved on July 19, 1985 for the following indications: lower respiratory tract infections, skin and skin structure infections, urinary tract infections (both uncomplicated and complicated), bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections, and central nervous system infections. The drug substance, ceftazidime is currently manufactured by GlaxoSmithKline (GSK). The RLD, FORTAZ[®] for Injection, is also manufactured by GSK. In this submission, the Applicant proposes to manufacture their product using the GSK product FORTAZ[®] in ADD-Vantage[®] 1 g and 2 g vials as the RLD.

The Applicant states that there are many similarities between the ADD-Vantage[®] System and the Duplex[®] System, making it the appropriate choice for the RLD. The Add-Vantage[®] vial is administered solely by the intravenous route as is the Duplex finished product. The Applicant is seeking approval for Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex[®] Container for the same indications approved for FORTAZ[®] for Injection with the exception of the urinary tract infection indication and intramuscular administration.

2.1 Product Information

Ceftazidime for Injection USP and Dextrose Injection USP in the dual chamber DUPLEX container is supplied for intravenous administration in strengths equivalent to 1 g and 2 g of ceftazidime. Ceftazidime for Injection USP is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. Sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity.

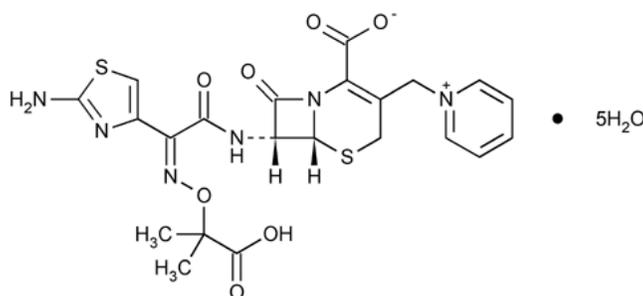
The DUPLEX container is a flexible dual chamber container. After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use. Each 50 mL contains ceftazidime pentahydrate equivalent to either 1 gram or 2 grams of ceftazidime. Solutions of Ceftazidime for Injection, USP and Dextrose Injection, USP range in color from light yellow to amber. The solution is intended for intravenous (IV) use only.

The DUPLEX Container is latex-free, PVC-free, and Di (2-ethylhexyl) phthalate (DEHP)-free. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

Clinical Review
Alma C. Davidson
NDA 50-823

Ceftazidime for Injection, USP and Dextrose Injection, USP in Duplex[®] Container

Chemical structure:



Chemical formula: C₂₂H₃₂N₆O₁₂S₂

Molecular weight: 636.6

Dosage Strength: 1 g or 2 g

Applicant's proposed indications, dosing regimens, age groups:

Ceftazidime for Injection and Dextrose Injection in the Duplex[®] Container has the same indications and dosing regimens as the RLD, FORTAZ[®] with the exception of the urinary tract infection indication and intramuscular administration.

2.2 Tables of Currently Available Treatments for Proposed Indications

No new proposed indications are included in this application. Some of the parenteral cephalosporin antibacterials available on the market that have similar indications as ceftazidime are listed in the table below:

Table 1: List of Parenteral Cephalosporins

| Cephalosporins | Indications |
|----------------|--|
| Ceftriaxone | <ul style="list-style-type: none"> -Lower respiratory tract infections -Skin and skin-structure infections -Urinary tract infections (uncomplicated and complicated) -Pelvic inflammatory disease -Bacterial septicemia -Bone and joint infections -Intra-abdominal infections -Meningitis |
| Cefazolin | <ul style="list-style-type: none"> -Respiratory tract infections -Urinary tract infections - Skin and skin structure infections -Biliary tract infections -Bone and joint infections -Genital infections -Septicemia -Endocarditis |
| Cefotaxime | <ul style="list-style-type: none"> -Lower respiratory tract infections -Genitourinary infections -Gynecologic infections -Bacteremia/septicemia -Skin and skin structure infections -Intra-abdominal infections -Bone and/or joint infections -Central nervous system infections |
| Cefuroxime | <ul style="list-style-type: none"> (b) (4) -Skin and skin-structure infections -Urinary tract infections (b) (4) (b) (4) (b) (4) |
| Cefoxitin | <ul style="list-style-type: none"> -Lower respiratory tract infections -Urinary tract infections -Intra-abdominal infections -Gynecological infections -Bone and joint infections -Septicemia -Skin and skin structure infections |
| Cefotetan | <ul style="list-style-type: none"> -Urinary tract infections - Lower respiratory tract infections - Skin and skin-structure infections -Gynecologic infections -Intra-abdominal infections -Bone and joint infections |
| Cefepime | <ul style="list-style-type: none"> -Pneumonia -Uncomplicated Skin and skin-structure infections -Urinary tract infections (uncomplicated and complicated) -Empiric therapy for febrile neutropenic patients -Complicated intra-abdominal infections |

Several cephalosporin antibacterials in the Duplex container have been marketed since 2000, as shown in the table below:

Table 2: List of Approved Cephalosporins in Duplex Container

| CEPHALOSPORIN | NDA | DATE OF APPROVAL |
|---|------------|-------------------------|
| Cefazolin for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 50-779 | July 27, 2000 |
| Cefuroxime for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 50-780 | February 21, 2001 |
| Cefotaxime for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 50-792 | July 29, 2004 |
| Ceftriaxone for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 50-796 | April 20, 2005 |
| Cefoxitin for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 65-214 | March 10, 2006 |
| Cefotetan for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 65-430 | August 9, 2007 |
| Cefepime for Injection, USP and Dextrose Injection, USP in Duplex [®] container | 50-821 | May 6, 2010 |

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, ceftazidime is marketed as FORTAZ[®] for injection in the United States. FORTAZ[®] has been available on the U.S. market since 1985 for the following indications: lower respiratory tract infections, skin and skin structure infections, urinary tract infections (both uncomplicated and complicated), bacterial septicemia, bone and

joint infections, gynecologic infections, intra-abdominal infections, and central nervous system infections

2.4 Important Safety Issues With Consideration to Related Drugs

There are no safety or effectiveness concerns with pharmacologically related products. Recent labeling changes with other cephalosporins included changes to the WARNINGS section and PRECAUTIONS/Information for Patients subsection regarding *Clostridium difficile* associated diarrhea (CDAD) as requested by the Agency in a letter to Sponsors dated September 29, 2006. On September 19, 2006, text regarding the potential interaction between ceftazidime and oral contraceptives in the PRECAUTIONS/ Drug Interactions section was added.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

No pre-submission regulatory activity occurred between the Applicant and the Division of Anti-infective and Ophthalmology Drug Products (DAIOP) regarding this application.

2.6 Other Relevant Background Information

The Applicant does not have any history marketing Ceftazidime Injection and Dextrose Injection in the Duplex[®] container.

3 Ethics and Good Clinical Practices

Not applicable.

3.1 Submission Quality and Integrity

Not applicable.

3.2 Compliance with Good Clinical Practices

Not applicable.

3.3 Financial Disclosures

Not applicable. No new clinical studies were conducted for this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Note: The reader is referred to the CMC review by the chemistry reviewer, Dr. Milton Sloan for detailed descriptions of the drug product and manufacturing process.

4.2 Clinical Microbiology

Note: The reader is referred to the microbiology review by the microbiology reviewer, Kerian Grande for details.

4.3 Preclinical Pharmacology/Toxicology

There are no additional non-clinical toxicology studies conducted to support this application.

4.4 Clinical Pharmacology

There are no new clinical pharmacology data submitted with this application. Ceftazidime for Injection and Dextrose Injection in Duplex[®] Container contains the same active ingredient as the reference listed drug, FORTAZ[®] (ceftazidime for Injection) by GSK. The Clinical Pharmacology reviewer, Yongheng Zhang, Ph.D., concluded that the Applicant met the requirements for waiver of evidence of in vivo bioavailability, based on the criteria listed in 21 CFR §320.22(b)(1)(i-ii). (Note: The reader is referred to the clinical pharmacology review for details.)

4.4.1 Mechanism of Action

Ceftazidime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

4.4.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this application.

4.4.3 Pharmacokinetics

The pharmacokinetic data are the same as the RLD, FORTAZ[®] (ceftazidime for Injection).

5 Sources of Clinical Data

This 505(b)(2) application contains no new clinical studies.

5.1 Tables of Studies/Clinical Trials

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

5.2 Review Strategy

Safety was reviewed based on recent literature publications relevant to clinical safety of ceftazidime and dextrose solution as provided by the Applicant. The reviewer conducted a separate search of the literature regarding the safety profile of ceftazidime injection and dextrose solutions related to human use. The Office of Surveillance and Epidemiology (OSE)-Division of Pharmacovigilance II was consulted for analysis of selected adverse drug reactions associated with ceftazidime in the Adverse Event Reporting System (AERS) database based upon the literature article by Steadman et al which is discussed later in this review.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable.

6 Review of Efficacy

There are no new clinical studies conducted by the Applicant to support this 505(b)(2) NDA for Ceftazidime for Injection Dextrose Injection in the Duplex[®] Container. The review for this NDA relies on prior FDA determination of effectiveness based on studies not conducted by or for the Applicant, B. Braun Inc., for the reference listed drug, FORTAZ[®].

Efficacy Summary

Not applicable.

6.1 Indication

Not applicable.

6.1.1 Methods

Not applicable.

6.1.2 Demographics

Not applicable.

6.1.3 Subject Disposition

Not applicable.

6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

The Applicant was requested to provide a safety update for ceftazidime with this submission. The Applicant performed a search of the literature using PubMed and looking for citations referencing “ceftazidime and safety or adverse events in humans” from August 12, 2009 to August 29, 2010. Recent literature publications regarding the safety of ceftazidime were submitted and reviewed by the Applicant and clinical reviewer. In addition, the Division consulted the Office of Surveillance and Epidemiology (OSE) for reports in AERS related to safety of ceftazidime focusing on renal adverse events. This request was based on conclusions by the Applicant’s safety reviewer, (b) (4), on a literature report by Steadman et al.²

As in past applications, the Applicant also looked at literature publications for other cephalosporins in Duplex container to support the possible contraindication to use of dextrose in patients with hypersensitivity to corn products.

Safety Summary

The safety update for ceftazidime included recent literature publications that addressed its safety profile during the period stated. Two of several publications had relevant clinical safety information for ceftazidime. The other publications did not provide relevant clinical safety information for ceftazidime. Therefore, these publications are not included in this review.

7.1 Methods

The Applicant reviewed the literature publications from the period indicated above. Of the articles obtained, two were selected by the Applicant’s safety reviewer as having clinical safety information relevant to ceftazidime. Other articles did not provide clinical information that could impact the safety (and labeling) of ceftazidime.

MO Comment: Medical publications with clinical relevance to the safety of ceftazidime were reviewed. Review of the other citations contained no information relevant to the clinical safety of ceftazidime.

Review of literature articles that discuss the clinical safety profile of ceftazidime:

- Hubert D, Le Roux E, Lavrut T, Wallaert B, Scheid P, Manach D, Grenet D, Sermet-Gaudelus I, Ramel S, Cracowski C, Sardet A, Wizla N, Deneuille E, Garraffo R. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother.* 2009 Sep;53(9):3650-6.

This paper reports on a multicenter, randomized crossover study comparing the safety and efficacy of continuous infusion with multiple short infusions of ceftazidime in patients with cystic fibrosis. Patients with chronic *Pseudomonas aeruginosa* colonization received two successive courses of intravenous tobramycin and ceftazidime (200 mg/kg of body weight/day) for pulmonary exacerbation. The ceftazidime was administered as thrice-daily short infusions or as a continuous infusion. The primary endpoint was the variation in the forced expiratory volume in 1 s (FEV₁) over the course of antibiotic treatment. Sixty-nine of the 70 patients enrolled in the study received at least one course of antibiotic treatment. The improvement in FEV₁ at the end of therapy was not statistically different between the two treatment procedures (7.6% after continuous infusion (CI) and 5.5% after short infusions (SI) but was better after continuous ceftazidime treatment in patients harboring resistant isolates ($P < 0.05$). The susceptibility profiles of the *P. aeruginosa* isolates remained unchanged and were similar for both regimens.

The study reported 124 adverse events (68 during the ceftazidime SI and 56 during the ceftazidime CI) in 50 patients. Only two of these events were considered to be severe adverse events requiring hospitalization for pulmonary exacerbation (one after the SI of ceftazidime and one after the CI of ceftazidime). The most frequent adverse events were abdominal pain, nausea and diarrhea (12%), hemoptysis (11.3%), headaches (7.3%), pulmonary exacerbations (6.5%), and tonsillitis (6.5%). The C-reactive protein concentration and the white blood cell count decreased significantly at the end of each antibiotic course for both regimens. The aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) levels increased significantly at the end of the antibiotic course, with no statistically significant difference between the two regimens being detected. No significant changes in the alkaline phosphatase and the gamma-glutamyl transferase levels were observed

The authors concluded that continuous infusion of ceftazidime did not increase its toxicity and appeared to be as effective as short infusions in patients with cystic fibrosis as a whole, particularly in patients harboring resistant isolates of *P. aeruginosa*.

MO Comment: The GI adverse events including abdominal pain, nausea, diarrhea and elevations of liver enzymes reported in this article are included in the ceftazidime label. Pulmonary exacerbations, hemoptysis, and tonsillitis are clinical manifestations related to cystic fibrosis, and unlikely related to ceftazidime. Decreased C-reactive protein (CRP) and WBC count could indicate diminished infection after the antibiotic treatment.

(b) (4)

(b) (4)

- Steadman E, Raisch DW, Bennett CL, Esterly JS, Becker T, Postelnick M, McKoy JM, Trifilio S, Yarnold PR, Scheetz MH. Evaluation of a potential clinical interaction between ceftriaxone and calcium. *Antimicrob Agents Chemother.* 2010 Apr;54(4):1534-40.

This article describes the author's approach to evaluating whether there were an excess number of embolic events related to ceftriaxone which could be potentially caused by ceftriaxone-calcium precipitates and used ceftazidime calcium as a comparator. The authors conducted a search of the medical literature for reports of ceftriaxone-calcium precipitation in adults and the FDA MedWatch Adverse Event Reporting System (AERS) databases for adverse drug reactions reported with ceftriaxone treatment in association with calcium. For comparison, the authors searched AERS for interactions reported between ceftazidime and calcium.

One hundred four adverse drug events (ADEs) with ceftriaxone-calcium and 99 events with ceftazidime-calcium were identified. The ADEs were further assessed for the possibility that the ADE was related to an embolic event and caused pulmonary or renal failure/damage. The events were categorized as probable embolic events if renal or pulmonary involvement could be related to an embolic event and ceftriaxone or ceftazidime were a primary or secondary drug in combination with calcium as a primary, secondary, or concomitant drug. Possible embolic events were categorized as renal or pulmonary involvement that could be related to an embolic event. Unlikely embolic events were instances of renal or pulmonary involvement where no clear relationship with an embolic event was evident. For ceftriaxone-calcium-related adverse events, 7.7% and 20.2% of the events were classified as probable and possible for embolism, respectively. Ceftazidime-calcium resulted in fewer probable embolic events (4%) but more possible embolic events (30.3%).

The authors stated that ceftazidime was used as a comparator of the associated but likely noncausal precipitation events. While the listed renal and pulmonary events are nonspecific for identification of embolic events, the "noise" created by this method is high in the ceftazidime group, signifying that most reactions observed are probably unrelated to the administration of the drugs in combination with calcium. The authors concluded that their analysis suggests a lack of support for the occurrence of ceftriaxone-calcium precipitation events in adults. The results of their analysis reinforce the revised FDA recommendations suggesting that patients >28 days old may receive ceftriaxone and calcium sequentially and provide a transparent and reproducible methodology for such evaluations.

MO Comment: Based on the conclusions of this article focusing on ceftriaxone-calcium interaction, it is difficult to establish whether a causal relationship of the possible embolic events were due to ceftazidime in combination with calcium or the presence of confounders or ceftazidime alone.

The Applicant's safety consultant recommended labeling changes, including new wording for renal toxicity (a labeled event) for ceftazidime label.

The Division consulted OSE-Division of Pharmacovigilance II (DPV II) to conduct an analysis of Adverse Event Reporting System (AERS) reports of renal adverse events associated with ceftazidime. The safety evaluator, Ronald Wassel, PharmD reviewed 20 cases of acute renal failure in association with ceftazidime. Based on his review, he concluded that the temporal association, and the reported association of renal impairment with ceftazidime, and toxic nephropathy with cephalosporins in general, it is reasonable to conclude that the renal impairment induced by ceftazidime may be severe and result in acute renal failure. Therefore, DPV II finds the Applicant's proposed change to the POSTMARKETING EXPERIENCE section of Ceftazidime for Injection, USP and Dextrose Injection, USP in Duplex[®] Container label regarding renal failure acceptable, but suggests the following wording (add the word which): "nephropathy, which may be severe (e.g., renal failure)."

(Note: The reader is referred to the consultation review of Ron Wassel, PharmD for details.) The clinical reviewer concurs with the proposed labeling text of the safety evaluator.

Based on Steadman's article, the other listed AEs including [REDACTED] (b) (4) [REDACTED] were non-specific for identification of embolic events. According to these authors, the "noise" created by their study method was high in the ceftazidime group which indicating that most of these reactions observed were probably unrelated to the administration of the drugs in combination with calcium. In the context of the study objectives in this paper, these AEs should not be included in the ceftazidime label at this time.

Review of selected literature publications on dextrose (corn) allergy:

The Applicant looked at archival and recent literature publications on dextrose or corn allergy to support the possible contraindication of dextrose containing solutions, such as the proposed Ceftazidime for Injection and Dextrose Injection in Duplex[®] Container, in patients with a history of corn allergy (see Table 3 and summary of cases below).

Table 3: Summary of Literature reported cases of allergic reactions to Dextrose (corn sugar) and Corn products

| AUTHOR(S) | CASES/ AGE /GENDER | MEDICAL HISTORY | CLINICAL FINDINGS | FOOD TEST (CORN) | DEXTROSE SOLUTION CHALLENGE | TREATMENT & OUTCOME AFTER CHALLENGE TEST |
|---|--------------------------|---|--|------------------------|--|--|
| Randolph TG, Rollins JP, Walter CK. | Case 1: 22/F | Asthma; allergic rhinitis; chronic fatigue | Sneezing Pruritus Urticaria Abdominal cramps Fatigue Neck pain | Positive | Positive (challenge +rechallenge) | Corn product elimination Recovered |
| | Case 2: 30/F | Irritable colon | Headache, posterior cervical myalgia, generalized aching; Episodic nausea, vomiting, diarrhea | Positive | Positive | Recovered |
| | Case 3: 54/F | Intermittent headaches | Headache, dizziness weakness, alternating constipation diarrhea, chronic dermatitis | Positive | Positive | Recovered after 2 days |
| | Case 4: 37/F | Chronic perennial nasal allergy | First challenge test developed angioedema but reported stable | Positive | Positive (challenge + rechallenge) | Recovered after a day |
| | Case 5: 41/M | Recurrent headache Rhinitis | Right frontal area pressure sensation, scotomas, inability to focus his eyes, neck pain, fatigue, nausea, and diarrhea. | Positive | Positive | Recovered after avoidance of corn |
| Sandberg DH. | 13/F | Chronic persistent abdominal pain | Nausea, vomiting, and weight loss | Positive | Positive | Avoidance of corn Recovered. |
| Liu W, Nixon RL. | 44/F | Chronic hand dermatitis Asthma (Note: No history of dietary corn allergy) | Tingling & itchy sensation in her hands | N/A | N/A | Prick testing positive to corn Avoidance to cornstarch powdered gloves |

These literature publications on dextrose or corn allergy are summarized below:

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: The patient is a 22-year-old woman who has a history of intermittent asthma since childhood, acute GI upsets since age 15, and perennial allergic rhinitis and chronic fatigue since age 19. In the months of July and August for the preceding two years, she 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. Following ingestion of USP dextrose, the patient developed acute reactive symptoms. Two years later, the patient received 25 mL 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 mL 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 with a history of constant headache, posterior cervical myalgia, and generalized aching for three years and episodic nausea, vomiting, and diarrhea for eight years was first noted when to have hypersensitivity to administration of corn syrup 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 the right side of her chest and midback; at three hours, an increase in nausea and diarrhea developed; and 3½ 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 off intravenous dextrose infusions. These acute reactions were repeated during several hospitalizations with receipt of dextrose solutions intravenously. A corn sugar test was performed and revealed similar acute reactive symptoms, while an isotonic sodium chloride solution test failed to elicit such reactions.

Case #3: This is a 54-year-old housewife with a history of intermittent headaches for 15 years, constant headaches associated with dizziness for 10 years and complaints of weakness, alternating constipation and diarrhea, and chronic dermatitis in her hands. Had a food test showing 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 a small amount of corn contained as an excipient in pharmaceutical tablets and ingestion of dextrose encountered by accident in commercially prepared foods caused symptoms. She received an intravenous injection of 5% dextrose as previously described for other cases. A few minutes later, she developed drowsiness, muscle pain over her neck and extremities, sniffing, coughing, lacrimation, headache and generalized fatigue. Her symptoms gradually tapered off during the following two days.

Case #4: A 37-year-old woman with a chronic history of perennial nasal allergy with intermittent nasal obstruction, other acute exacerbation of symptoms such as sore throat and enlargement of anterior cervical glands 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 a test infusion of 25 mL 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 mL 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 with a two-year history of recurrent headaches and rhinitis had symptoms including 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 cutaneous allergy testing, he reacted to house dust and individual food tests revealed corn sensitivity. With dust therapy and avoidance of corn, the patient reported a complete relief of his symptoms lasting for several weeks. He then underwent the intravenous 5% dextrose infusion test and a few minutes later, developed a 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.

MO Comment: These five cases describe atopic patients experiencing a wide variety of symptoms ranging from nonspecific symptoms (i.e., headaches, neck pain, fatigue) to specific respiratory (nasal allergy, rhinitis) and gastrointestinal (nausea, diarrhea) signs and symptoms. Food testing confirmed their hypersensitivity reactions to corn. Challenge and rechallenge testing with corn derived dextrose solution elicited positive allergic reactions. Avoidance of dietary corn resulted in relief of symptoms.

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 describes four cases 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 cubic centimeters of 5% dextrose resulted in severe constitutional symptoms clinically similar to those observed following the ingestion of corn meal and corn sugar.

MO Comment: This abstract describes four patients with corn sensitivity. It is not stated in this abstract whether these four cases of corn sensitivity 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 and weight loss for two months. An exploratory surgery with appendectomy was performed because of chronic persistent abdominal pain and revealed no apparent abnormality. The patient developed nausea and vomiting of 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, additional foods were gradually added to her diet and were tolerated except for corn products. Intradermal provocative food testing with corn extract produced symptoms suggesting corn sensitivity. Intravenous administration of 25 ml of 5% dextrose with water reproduced all her previous GI symptoms. Corn syrup and corn meal produced nausea and vomiting three hours after ingestion and were associated with acute alteration and decrease in plasma C3 complement concentration. Laboratory results including C3 were low with elevated serum IgE and IgM. The patient gained weight in three weeks after avoiding corn products and had no recurrence of her GI symptoms.

MO Comment: This case report describes a hypersensitivity reaction (probably Type I with elevated IgE) to dietary corn products (corn syrup and corn meal). A challenge test with intravenous dextrose administration revealed a positive reaction.

4. Liu W, Nixon RL. Corn contact urticaria in a nurse. *Australas J Dermatol.* 2007 May;48(2): 130-1.

This is a case report of a 33-year-old ICU nurse who presented with a 12-year history of hand dermatitis. She has a history of asthma and seasonal hay fever. She described an intermittent itchy, blistering eruption on her hands which improved away from work. She also describes an "itchy throat" when she eats bananas, avocado, kiwi fruit, and cantaloupe. She was advised to avoid latex gloves and 'latex-fruits'. She switched from

wearing latex gloves to nitrile gloves. She reported a tingling and itchy sensation in her fingers immediately after wearing both powdered and non-powdered nitrile gloves. It was reported that despite avoidance of latex, her hand dermatitis had failed to improve. A patch test was performed which was negative. She also had reaction to nickel and cobalt (relevance was presumed to be old). A prick testing was performed which showed a strong reaction to corn with relevance to cornstarch powder, but negative reaction to latex. The patient reports no dietary reaction to corn. The patient was advised to avoid gloves containing cornstarch powder and recommended an Ansell® non-powdered disposable nitrile glove, which contains no cornstarch. Ansell does not use corn starch in the production of their latex and non-latex powder-free gloves. She was advised to avoid latex products. Her hand dermatitis cleared following avoidance of cornstarch powder. Three months later, her hand dermatitis recurred in the setting of frequent hand washing after care of a patient with melena. The patient was diagnosed with corn contact urticaria, irritant contact dermatitis and type I hypersensitivity to latex fruits.

MO Comment: This article reports an atopic patient who developed chronic contact dermatitis associated with cornstarch powder in gloves. It is notable that this patient reported no reaction to dietary corn. There was no report of hypersensitivity to corn-derived dextrose solution in this case.

In addition, the reviewer performed a search in the PubMed, Embase, and Web of Science databases for published articles to support the possible dextrose contraindication in the ceftazidime label. The reviewer found two relevant articles regarding anaphylactic reaction to dextrose solution. One article described a case with known history of corn allergy who developed anaphylaxis to dietary corn observed in a double-blind, placebo-controlled food challenge.

1. Guharoy SR, Barajas M. Probable anaphylactic reaction to corn-derived dextrose solution. *Vet Hum Toxicol* 1991 Dec;33(6):609-10.

This is a case report of a 23-year-old woman who was admitted to the hospital at term gestation for repeat cesarean section. The patient had been on no medication other than prenatal vitamins. She had a known allergy to both codeine and tetracycline. The patient's history revealed no prior food allergy and an uncomplicated pregnancy. During the peripartum period, intravenous fluid therapy was begun consisting of 5% dextrose Lactated Ringer's. No other medications were given at this time. Within 8 minutes after initiation of fluid therapy the patient experienced anaphylactic reaction, including orofacial swelling, difficulty in breathing, hypotension (BP 70/40), and frequent premature ventricular contractions. Other symptoms included hoarseness of voice, total body warmth and flushing. The patient's treatment consisted of immediate discontinuation of the intravenous solution (dechallenge) along with the initiation of plain Lactated Ringer's IV solution, diphenhydramine 25 mg IV and hydrocortisone 100 mg IV. The plain Lactated Ringer's solution was continued with no apparent adverse

effects. The report states that the patient subsequently delivered a viable male infant with an Apgar score of 6 at 1 min and 9 at 5 min. The operative course was unremarkable with the patient doing well postoperatively. The IV diphenhydramine 50 mg every 6h and hydrocortisone 100 mg every 6h were continued for 24 h. The patient was subsequently discharged with infant, both in satisfactory condition. The patient was also warned of possible anaphylaxis to dextrose solutions in the future. The suspect solution was sent to the manufacturer for analysis for contamination, but no contaminant was reported.

According to this case report, the causative agent was suspected to be the corn-derived dextrose found in the IV solution. Since the patient did not receive any drugs prior to the anaphylactic event and the IV fluid contained no preservative or dye, the authors concluded that the reaction was due to corn allergy.

MO Comment: This case describes a patient with no history of food allergy who developed an anaphylactic reaction following receipt of 5% dextrose Lactated Ringer's solution. The dextrose solution was reported to be corn-derived. Based on this finding, this was probably a case of corn induced allergic reaction. No information on skin testing was reported in this article.

2. Czarny D, Prichard PJ, Fennessy M, Lewis S. Anaphylactoid reaction to 50% solution of dextrose. Med J Aust. 1980, 2:255-258.

This article reports on two patients with a history of extrinsic asthma and insulin-dependent diabetes mellitus who experienced anaphylactoid reactions after administration of a 50% solution of dextrose intravenously.

Case 1: A 67-year-old man with a history of extrinsic asthma since his early twenties and diabetes mellitus since 42 years of age was reported to be unconscious but with normal breathing and was brought to the hospital. His medications included NPH insulin (24 units in the morning), regular insulin (20 units in the morning), salbutamol (metered aero 0.2 mg four times a day), beclomethasone (metered aerosol, 0.1 mg four times a day) and oral betamethasone 1 mg in the morning. A provisional diagnosis of hypoglycemia was made and the patient was given 50 mL of 50% dextrose solution intravenously. Apparently, the patient regained consciousness within one minute, but immediately developed respiratory distress associated with sweating and vomiting. The patient was intubated. His ventilation was reported to be difficult and characterized by scattered rhonchi on auscultation. Intravenous injections of salbutamol, aminophylline, and hydrocortisone apparently relieved the airway obstruction. The patient was admitted to the ward and continued to improve with no respiratory difficulty. About three days after admission, the patient was noted to become pale and sweaty with incoherent speech. A dextrostix test confirmed hypoglycemia. Once again, the patient was given 50 mL of 50% solution of dextrose intravenously. Within 2 to 3 minutes, he became cyanotic, sweaty, with associated respiratory distress and rhonchi on auscultation. His

symptoms were relieved with intravenous aminophylline 250 mg and hydrocortisone 100 mg, and 2 mL of 0.5% salbutamol by nebulizer.

Case 2: This is an 8-year-old girl with a 7-year history of extrinsic asthma, allergic rhinitis and eczema, and four-year history of insulin-dependent diabetes mellitus. Her medications included Actraped insulin (30 units), Monotard insulin (24 units) in the morning, salbutamol metered aerosol, 0.2 mg three times a day, and theophylline oral 125 mg twice a day. The patient's diabetes had been unstable with frequent episodes of hypoglycemia and ketoacidosis which necessitated hospital admissions. Her hypoglycemic episodes were treated with intramuscular administration of glucagon until the age of six years. Since that time, 50% dextrose solution had been used in doses of 10 mL to 50 mL intravenously, and on the 4 occasions when dextrose has been given, the patient developed rhinorrhea, perinasal and periorbital edema, and asthma within 2 to 3 minutes after dextrose administration. The report states that on each successive occasion, her symptoms became more severe. The patient's asthma usually responded to salbutamol aerosol but her facial swelling and rhinorrhea persisted for 2 or 3 days.

The authors conducted further investigation to determine the cause of this reaction. The effect of varying concentrations of dextrose on histamine content of the blood in normal, allergic, non-diabetic, and diabetic, and non-allergic patients was studied. According to the report, preliminary results suggest that the higher concentrations of dextrose induced increased histamine release from blood cells. This finding was more marked in two diabetics, particularly diabetic-allergic patients and in one diabetic who was receiving a beta-adrenoreceptor blocking agent. The mechanisms of the reported reactions remain uncertain and more investigations are necessary.

MO Comment: In both cases, the patients were atopic with diabetes mellitus and experienced anaphylactic reactions after receiving 50% dextrose solution. Information regarding the derivative of the dextrose solution and patient's history of allergy to corn or any corn products was not provided in this article.

3. Tanaka LG, El-Dahr JM, Lehrer SB. Double-blind, placebo-controlled corn challenge resulting in anaphylaxis. *J Allerg Clin Immunol* 2001; 107(4): 744

This is a case report of a 44-year-old woman who was referred for evaluation of corn allergy. Her first reaction to corn (1982) consisted of an oral tingling sensation after licking corn meal from her fingers. The symptoms resolved without medical intervention. However, since 1994, with limited exposure she has had 4 reactions to corn requiring emergency department visits for pruritus, urticaria, vomiting, and diarrhea. The most recent reaction, 6 months previously, also involved difficulty breathing; subsequently, she avoided corn and corn products. The patient developed urticaria, vomiting, and diarrhea in response to pecans and peanuts and therefore carries injectable epinephrine. She received immunotherapy years ago for allergic rhinitis (now treated with nasal budesonide and fexofenadine). She had never had asthma, eczema, or adverse

reactions to medications, latex, or insect stings. Her environmental history was unremarkable. She has smoked a half pack of cigarettes per day for 30 years and currently takes bupropion hydrochloride. Her siblings have allergic rhinitis. Her other medical problems include gastroesophageal reflux disease and hypercholesterolemia, treated with omeprazole and simvastatin, respectively. Antihistamines were discontinued 1 week before her evaluation. Except for enlarged, pale nasal turbinates, her physical examination findings were normal. Baseline peak flow measurements averaged 460 (L/min).

The patient came to the General Clinical Research Center for evaluation. Skin prick testing revealed positive results for histamine (10 mm), cooked corn (10 mm), uncooked corn (35 mm), corn pollen (39 mm), peanut (28 mm), rice (20 mm), grass mix (20 mm), and dust mites (25 mm). Negative test responses occurred for PBS, lentil, challenge vehicle, wheat, milk, soy, shrimp, egg, oat, rye, ragweed, oak, cat, dog, and molds. The research center prepared the corn, placebo, and challenge vehicle extracts; the rest were from Greer. The challenge consisted of 2 phases; corn flour (baked ground corn kernels) or placebo (baked ground lentils), where incremental amounts were given at 30-minute intervals. The corn flour or placebo was mixed with applesauce, apple juice, peach puree, and sugar to mask the taste. The 2 phases were separated by 2 hours. Neither the patient nor the physician knew the challenge sequence:

- a. During the first phase the patient did not have subjective or objective reactions.
- b. After a 2-hour break, she underwent the second phase of the challenge (corn flour), and a reaction occurred. After receiving the first dose of corn (2 g), she described feeling “fullness,” but her vital signs and peak flow remained at baseline levels. After the second dose of corn (8 g), she reported mild throat pruritus that resolved, but no objective changes were observed. Thirty minutes after the third corn dose (16 g), erythematous sclera, nasal congestion, and generalized urticaria developed. She was given diphenhydramine and observed. Fifteen minutes later, classic signs of anaphylaxis developed, including hypotension (systolic 99 mm Hg/diastolic 53 mm Hg), tachycardia (126 bpm), vomiting, and wheezing. According to the report, tryptase level could not be documented. Treatment with epinephrine, oxygen, albuterol, methylprednisolone, and intravenous fluids commenced immediately. She was admitted to the General Clinical Research Center overnight for continued observation. By morning her symptoms had resolved, and her vital signs had returned to baseline for several hours. She was discharged in good condition and reported no ill effects thereafter. On follow-up, she remained well and without further problems.

MO Comment: This article describes a patient with known history of corn allergy who developed anaphylaxis to dietary corn observed in a double-blind, placebo-

controlled food challenge. No information regarding the patient's allergy to parenteral corn products was provided. Although literature reports of corn allergy are rare, in some patients with known hypersensitivity reactions to corn or corn derived products, severe allergic reactions (i.e., anaphylactic reactions) can develop. Health care professionals should be aware or cautioned of the potential risk of such reactions in patients with known allergy to corn or corn-derived products.

Search of the FDA Adverse Event Reporting System (FAERS):

This search was conducted in order to determine if any additional reports of serious adverse reactions (i.e., anaphylaxis, anaphylactic reactions) related to dextrose solutions have been received by the FDA. Search for dextrose with the Standardized MedDRA Query (SMQ) for Anaphylactic Reaction included preferred terms (PTs). Search terms were narrowed to anaphylaxis and/or anaphylactic reactions/shock, allergic reactions and type I hypersensitivity reactions. No particular date was performed in the search. The search retrieved a total of 108 cases which were provided by OSE-safety evaluator. After looking at the 108 cases, the reviewer found 22 suspected cases of dextrose associated serious adverse reactions. The reviewer excluded cases which listed multiple suspect medications including Dextran as primary suspect for anaphylaxis or anaphylactic reaction, sodium chloride solution as the single suspect drug, a probable acute transfusion reaction with septic shock, and one report with "unreadable" printed copy.

Table 4 summarizes the cases of serious adverse reactions (AEs) associated with dextrose solution from AERS.

Table 4: Cases in AERS with Serious AEs associated with Dextrose solutions

| Mfr. # (ISR#) Age/Gender/ Country/Source of report/ Manufacturer | Adverse event term(s) | Suspect medications/ concomitant medications | Dose/ indication/ Latency/ Therapy dates | Medical History | Patient Outcome /Causality assessment |
|--|-----------------------|---|---|--|--|
| 1) FDA Control Number: 532874 (Accession No. 88071100100181)/ 23y/ F/USA/Health professional/ Baxter-Travenol (MO Note: This case is reported in Guharoy article. ³) | Anaphylactic reaction | Dextrose 5% with Lactated Ringer's | 125 mL/hour/ 8 minutes of infusion/ June 27, 1988 | Patient admitted for repeat Caesarian section. | Recovered after treatment/ A Memorandum sent to Baxter-Travenol and after discussion of case with Baxter medical specialist, patient may have an allergy to dextrose derived from corn. |
| 2.) FDA Control Number: 757701 (Accession No. 91060700100431)/unknown/F/U SA/Abbott Laboratories (Note by MD reporter: Pt is #1 of 4 over the past 10 months who sustained this AE immediately upon startup of IV fluid.) | Anaphylactic reaction | Dextrose 5% injection, USP/ unknown | Unknown/ Unknown/ Unknown/ Unknown | Patient has history of latex allergy. | Unknown/ Unknown |
| 3.) FDA Control Number: 757703 (Accession No. 91060700100441)/unknown/F/U SA/Abbott Laboratories (Note by MD reporter: Pt is #2 of 4 over the past 10 months who sustained this AE immediately upon startup of IV fluid.) | Anaphylactic reaction | Dextrose 5% injection, USP/ Unknown | Unknown/ Unknown/ Unknown/ Unknown | Patient has history of latex allergy. | Unknown/ Unknown |
| 4.) FDA Control Number: 757703 (Accession No. 91060700100441)/unknown/F/U SA/Abbott Laboratories (Note by MD reporter: Pt is #3 of 4 over the past 10 months who sustained this AE immediately upon startup of IV fluid.) | Anaphylactic reaction | Dextrose 5% injection, USP/ Unknown | Unknown/ Unknown/ Unknown/ Unknown | Patient has history of latex allergy. | Unknown/ Unknown |
| 5.) FDA Control Number: 757703 (Accession No. 91060700100441)/unknown/F/U SA/Abbott Laboratories (Note by MD reporter: Pt is #4 of 4 over the past 10 months who sustained this AE immediately upon startup of IV fluid.) | Anaphylactic reaction | Dextrose 5% injection, USP/ Unknown | Unknown/ Unknown/ Unknown/ Unknown | Patient has history of latex allergy. | Unknown/ Unknown |

Table 4: Cases in AERS with Serious AEs associated with Dextrose solutions (cont.)

| Mfr. # (ISR#) Age/Gender/ Country/Source of report/ Manufacturer | Adverse event term(s) | Suspect medications/ concomitant medications | Dose/ indication/ Latency/ Therapy dates | Medical History | Patient Outcome /Causality assessment |
|--|--------------------------------|--|---|--|--|
| 6.) FDA Control Number: 737712 (Accession No. 91040700100041)/40y /F/USA/ Health Professional/Abbott Laboratories/ (Note: Duplicate to FDA CN# 757705) | Anaphylaxis | Dextrose 5% injection, USP/Unknown | Unknown/ To keep vein open/ 02/22/91/ few seconds at starting infusion. | History of anaphylaxis two years prior, occurred at startup of IV infusion of 5% dextrose. Pt was placed on a ventilator. History of asthma; allergy to latex gloves, X-ray dye, environmental allergens, cats, dogs, and nuts | Physician suspects latex as causal. Patient suspects IV bag. |
| 7)ISR #3081182-3-00/36y/F/USA/Health Professional/B.Braun Medical | Anaphylactoid reaction | Dextrose 5% & 0.45% NaCl injection | Hydration for hyperemesis/ Few seconds on starting the infusion/ 04/10/1998 | Patient is pregnant. No history of allergies. | Recovered/ Cause of reaction was unknown. |
| 8) ID# 5328089/42y/M/USA/ Medical College of Virginia Hospitals-Pharmacy Services | Anaphylactoid reaction (?) | Dextrose and hydrolysable saccharides & Glucose 5% in Water. | After infusion of dextrose on 12-10-70; the following day (12-10-70) after glucose tolerance test | Patient has arteriosclerotic heart disease. Patient has previous history of allergy resulting in hives of unknown cause. | Unknown/ Unknown. |
| 9) ID# 00055060/ 32y/F/USA/Nurse/ Cutter Laboratories | Anaphylactic shock (?) | Dextrose 5% in Lactated Ringers injection/ Elavil, Valium, colace, Multivitamin, Na bicarbonate, Oxygen 2-4 liters prn, Talwin, Demerol, & Macrochantin. | 2500 cc. daily/Unknown/ 03-04-73 | Patient has multiple sclerosis; legally blind; allergies to multiple medications (including barbiturates & thorazine). | Admitted to hospital with diagnosis of "acute vascular crisis with shock, possibly septicemia secondary to chronic urinary tract infection.; Pt. recovered & discharged to nursing home. |
| 10) FDA Control Number: 330874 (Accession No. 85020700100421)/ unknown/unknown/USA/ Unknown/Abbott (MFR Control # H01358) | Allergic-Anaphylactic reaction | 5% Dextrose & Lactated Ringer's/Unknown | Unknown/ Unknown | Unknown | Unknown/ Unknown |
| 11) MFR Control # S85041204 (Accession No. 8505070740024)/33y/F USA/RN/ Travenol Laboratories | Anaphylactic reaction | 5% Dextrose & 0.45% NaCl injection, USP in Plastic container/ Unknown | Unknown/ 10 minutes into the infusion/ 04/08/85 | Patient has "antibiotic-induced colitis"; no history of cardiac or respiratory disease. | Resolved completely within 30 minutes after change of IV solution. |

Table 4: Cases in AERS with Serious AEs associated with Dextrose solutions (cont.)

| Mfr. # (ISR#) Age/Gender/ Country/Source of report/ Manufacturer | Adverse event term(s) | Suspect medications/ concomitant medications | Dose/ indication/ Latency/ Therapy dates | Medical History | Patient Outcome /Causality assessment |
|---|-----------------------------|---|--|---|---|
| 12.) ISR: 6383744-4 (Case #7086702)/37/M/UK/Baxter (Case # 2009BH019686) Follow-up report to ISR: 6542589-2 | Anaphylactic reaction | 5% Dextrose/ Eloxatin (Oxaliplatin) (130 mg/m ²) | Approximately 30 mL and 20 minutes into start of infusion. | Rectal carcinoma | Recovered/ reporter believed AE as related to 5% glucose. |
| 13.)10066888-NA01-0 /11y/F/USA/Baxter (duplicate of case# 249429) | Anaphylactic reaction | 5% Dextrose injection, USP-1000 mL/sodium bicarbonate 30 mEq | Within minutes of 300 mL of dextrose IV/hydration for chemotherapy (methotrexate)/ 12/01/2004 | Acute lymphocytic leukemia; History of reaction to platelets. | Recovered after stopping the infusion. /Unknown |
| 14.) ISR: 6801214-3/80y/ Age unknown/F/UK/Baxter (MCN#: CA-Baxter 2010BH010020) | Anaphylactic reaction | Glucose (Dextrose) solution for intravenous infusion 5% (Baxter)/ Carboplatin 450 mg (Teva product) | Unspecified time, pt. experienced anaphylactic reaction | Bowel carcinoma | Recovered in hospital after a day/Unknown. |
| 15.) 08H-163-0315243-00/34y/F/USA/ Hospira | Anaphylactic reaction | Dextrose 5% injection, USP in Flexible Container/ no concomitant drugs | After completion of infusion of dextrose solution for hydration prior IVIG therapy/ Oct. 29,2008 | History of immune globulin (IVIG) therapy; other medical history is unknown | Recovered, and released from hospital that same day. / Unknown |
| 16.) FDA Control No. 1603014/70y/F/USA/ Health professional/Abbott Laboratories (MFR Control #: H 4006191 AO) | Anaphylaxis | Dextrose 5% Injection, USP/Unknown | Within 15 minutes after start of infusion/ Unknown/ 07-00-94 | Patient has allergy to corn and other foods | AE occurred at (b) (4) Unknown |
| 17.) FDA Control No. 1567534/8y/F/USA/ Health professional/Baxter Health Care (MFR Control #: S95020301 01) | Anaphylactic reaction | 5% Dextrose & 0.45% NaCl injection, USP | Unknown/ Hydration/ 5-10 minutes into infusion/ 02-02-95 | Pyelonephritis; History of previous anaphylactic reaction | Patient's symptoms apparently subsided with no medication needed at ER/Unknown. |
| 18.) FDA Control No. 1567534/8y/F/USA/ Health professional/Abbott Laboratories (MFR Control #: H 3006145 AO) | Anaphylactic reaction | 5% Dextrose & 0.225% NaCl /Unknown | Unknown | Unknown | Unknown |

Table 4: Cases in AERS with Serious AEs associated with Dextrose solutions (cont.)

| Mfr. # (ISR#) Age/Gender/ Country/Source of report/ Manufacturer | Adverse event term(s) | Suspect medications/ concomitant medications | Dose/ indication/ Latency/ Therapy dates or date of AE | Medical History | Patient Outcome /Causality assessment/ Comment |
|--|---------------------------|--|---|---|---|
| 19.) FDA Control Number: 136488 (Accession No. 82060700105001/27/ F/USA/ Pharmacist/Abbott Laboratories/ | "Shock-like" symptoms | 5% Dextrose in Water /Unknown | 500 ml./ immediately after start of infusion/ Keep vein open prior delivery/ 03-10-82 | Patient admitted for delivery. Pt. reported to have previous normal delivery and to be emotionally unstable with experience of shock-like symptoms during a sonogram, 24 hours prior current delivery. | Recovered. Examination of the fluid contents showed no endotoxins and impurities. Patient had normal delivery with a baby (Apgar score of 9)./ Report summary states that patient exhibited vasovagal reaction during venipuncture procedure. |
| 20.)10064898-NA01-0 /Age unknown/F/USA/ Baxter (Case # 241696) | Anaphylactic reaction | 5% Dextrose injection, USP in Standard Viaflex (LVP>150 mL) packaged in Di (2-ethylhexyl) phthalate (DEHP) container | Unknown/ 03/01/2004 | Unknown | Director of Pharmacy reported that the patient (employee of the pharmacy) developed anaphylactic reaction upon entering the IV room due to DEHP container of dextrose injection solution |
| 21.) ISR 3150559-X-00- 01/35y/F/USA/ Pharmacia & Upjohn/ McGaw/Health professional | Anaphylactic reaction | Solumedrol Sterile powder and D5W 250 mL (McGaw) | 5 minutes into infusion/ 1gm of solumedrol in 250 mL/ 03-14/1997 | Multiple sclerosis with blurred vision; multiple allergies: penicillin, codeine, IVP dye, demerol eggs, peanuts, legumes, etc) | Recovered/ Unknown/ Pt. received unspecified "steroids" in the past |
| 22.) 95192/33y/F/USA/ Health professional/ Unknown | "Anaphylaxis" reaction | Neupogen IV; and 5% Dextrose solution as diluent | 500 mcg daily IV; 5% Dextrose solution/ 12-26-1998 | Leukemia; No prior problems with Neupogen therapy | Recovered after stopping infusion/ Unknown |

MO Comment: The MO reviewed the 22 cases of serious adverse reactions with dextrose solution as suspect medications. One case of anaphylactic reaction possibly associated with dextrose solution (FDA Control Number: 532874; Accession No. 88071100100181) was also reported in the literature (Guharoy paper).

One report (#10064898-NA01-0/age unknown/USA/Baxter/#241696) was a puzzling case of anaphylactic reaction. The patient was apparently an employee of a pharmacy who developed an anaphylactic reaction upon entering the IV room with a DEHP container of dextrose injection solutions. An allergic type reaction is possible in this case; however, no information or medical history was reported. The patient was apparently treated and recovered.

It is notable that the reported manufacturers of the dextrose solutions were Cutter, Abbott, Baxter, B.Braun, and Hospira companies. It is unknown from majority of these cases whether the dextrose solutions were corn-derived.

No definite conclusions can be made from these cases because of the limited information regarding patient's history (including confounders), concomitant medications, and reporter's causality assessments. However, in two cases (FDA Control #: 532874; Accession No. 88071100100181 and FDA Control # 1603014), anaphylactic reaction and anaphylaxis, respectively, have occurred. These serious adverse drug reactions appear to be attributable to the administration of dextrose solution by causal and temporal association. The anaphylactic reaction in the first case was possibly caused by an allergic reaction to corn-derived dextrose solution. The second patient has known allergy to corn but no other details of the case reported.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

No studies were conducted for this submission. Literature articles were reviewed to provide the safety update for ceftazidime injection.

7.1.2 Categorization of Adverse Events

Not applicable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

Not applicable.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Not applicable.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

Not applicable.

7.3.1 Deaths

Not applicable.

7.3.2 Nonfatal Serious Adverse Events

Not applicable.

7.3.3 Dropouts and/or Discontinuations

Not applicable.

7.3.4 Significant Adverse Events

Not applicable.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

Not applicable.

7.4.1 Common Adverse Events

Not applicable.

7.4.2 Laboratory Findings

Not applicable.

7.4.3 Vital Signs

Not applicable.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

Not applicable.

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

The adverse events reported during the postmarket experience for ceftazidime are taken from the RLD, FORTAZ® label⁴:

“General: Anaphylaxis; allergic reactions, which, in rare instances, were severe (e.g., cardiopulmonary arrest); urticaria; pain at injection site.

Hepatobiliary Tract: Hyperbilirubinemia, jaundice.

Renal and Genitourinary: Renal impairment.”

9 Appendices

9.1 Literature Review/References

1. Hubert D, Le Roux E, Lavrut T, Wallaert B, Scheid P, Manach D, Grenet D, Sermet-Gaudelus I, Ramel S, Cracowski C, Sardet A, Wizla N, Deneuille E, Garraffo R. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother.* 2009 Sep;53(9):3650-6.
2. Steadman E, Raisch DW, Bennett CL, Esterly JS, Becker T, Postelnick M, McKoy JM, Trifilio S, Yarnold PR, Scheetz MH. Evaluation of a potential clinical interaction between ceftriaxone and calcium. *Antimicrob Agents Chemother.* 2010 Apr;54(4):1534-40.
3. Guharoy SR, Barajas M. Probable anaphylactic reaction to corn-derived dextrose solution. *Vet Hum Toxicol* 1991 Dec;33(6):609-10.
4. Czarny D, Prichard PJ, Fennessy M, Lewis S. Anaphylactoid reaction to 50% solution of dextrose. *Med J Aust.* 1980, 2:255-258.
5. Tanaka LG, El-Dahr JM, Lehrer SB. Double-blind, placebo-controlled corn challenge resulting in anaphylaxis. *J Allerg Clin Immunol* 2001; 107(4): 744.
6. Venter C, Skypala I, Dean T. Maize allergy: what we have learned so far. *Clin Exp Allergy.* 2008 Dec;38(12):1844-6. Epub 2008 Oct 18.

7. Van der Klauw MM, Wilson, JHP, Stricker BH..Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974-1994) and review of the literature. Clin Exp Allergy, 1996; 26,1355-1363.
8. FDA Adverse Event Reporting System (FAERS) database.
9. FORTAZ® (ceftazidime for injection) Full Prescribing Information.

9.2 Labeling Recommendations

The Applicant made the following changes to the Ceftazidime for Injection and Dextrose Injection in Duplex® Container in PLR format: **(MO Note: The clinical reviewer's proposed labeling revisions are highlighted in yellow in the attached label.)**

- Replacement of RLD, FORTAZ® by GSK specific information with B.Braun Medical Inc's product name, Ceftazidime for Injection and Dextrose Injection USP in Duplex® Container and IV route of administration.
- Deletion of all the text relating to (b) (4)
- Addition of text under CONTRAINDICATIONS section, regarding hypersensitivity to corn products: **(MO Note: Additions are underlined, and deletions are marked with strikethrough.)**

(b) (4)

MO Comment: Based on review of the available information regarding the ADEs (both serious and non-serious) possibly associated with use of corn-derived dextrose solutions, the reviewer proposes the following labeling changes:

Under the CONTRAINDICATIONS section:

"HYPERSENSITIVITY TO CORN PRODUCTS

Solutions containing corn-derived dextrose are contraindicated in patients with a known hypersensitivity to parenteral corn products, as rare serious allergic reactions have been reported.

- Addition of disclaimer and text under ADVERSE REACTIONS/Postmarketing Experience subsection:

“POSTMARKETING EXPERIENCE

“The following adverse reactions have been reported during postapproval use of ceftazidime. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to readily estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis; allergic reactions, which, in rare instances, were severe (e.g., cardiopulmonary arrest). Respiratory reactions, including hypoxia and respiratory arrest have been reported; nephropathy may be severe (e.g. renal failure); urticaria, pain at the injection site. Hyperbilirubinemia, jaundice, urticaria, pain at the injection site, decreased concentrations of C-reactive protein, renal impairment and disseminated intravascular coagulation have been reported.”

MO Comment: The first paragraph is a disclaimer text which was revised by the Applicant from the RLD, Fortaz[®] label which states:

“ In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with FORTAZ and were reported spontaneously. For some of these events, data are insufficient to allow an estimate of incidence or to establish causation.”

The Applicant’s proposed disclaimer statement is acceptable. Regarding the second paragraph and based on the consult from OSE-DPVII, the Applicant’s proposed change to renal failure is acceptable, but suggests the following wording (add the word which): “nephropathy, which may be severe (e.g., renal failure).”

Based on Steadman’s article, the other listed AEs including (b) (4) were non-specific for identification of embolic events. According to Steadman et al, the “noise” created by their study method was high in the ceftazidime group which indicates that most of these reactions observed were probably unrelated to the administration of the drugs in combination with calcium.

Based on Hubert's article, the AEs mentioned including (b) (4)

In the context of the article objectives, these AEs should not be included in the ceftazidime label at this time.

Therefore, the reviewer proposes the following labeling text for the second paragraph to be consistent with the RLD label, and adding the labeling text for renal failure as recommended by the OSE-Safety evaluator and the Applicant:

"General: Anaphylaxis; allergic reactions, which, in rare instances, were severe (e.g., cardiopulmonary arrest); urticaria; pain at injection site.

Hepatobiliary Tract: Hyperbilirubinemia, jaundice.

Renal and Genitourinary: Nephropathy, which may be severe (e.g., renal failure)."

- Addition of text under the DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING sections, regarding description of the DUPLEX[®] container.
- In the Pediatric Use subsection and under DOSAGE AND ADMINISTRATION section, the pediatric information has been removed in order to ensure consistency among all Duplex products .
- Minor editorial revisions (e.g., All "μ" for μg symbols in all tables have been replaced with "mc" to become "mcg"; addition of registered trademark symbol).
- Changed titles and subtitles as required for PLR format per Guidance for Industry, Labeling for Human Prescription Drug and Biological Products.

20 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Clinical Review
Alma C. Davidson
NDA 50-823
Ceftazidime for Injection, USP and Dextrose Injection, USP in Duplex[®] Container

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALMA C DAVIDSON
04/18/2011

JANICE K POHLMAN
04/19/2011

CLINICAL FILING CHECKLIST FOR NDA 50-823

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|------------|-----------|-----------|----------------|
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | √ | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | | √ | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | √ | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)? | | | √ | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | √ | | | |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | √ | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | √ | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | | | √ | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | √ | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | | √ | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | | | √ | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | √ | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | | | √ | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | √ | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | | | √ | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | | | √ | |

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: Clinical Filing Checklist for NDA 50-823

CLINICAL FILING CHECKLIST FOR NDA 50-823

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| | |
|------------------------------|-----------------|
| Alma C. Davidson, M.D. | October 1, 2010 |
| Reviewing Medical Officer | Date |
| Janice Pohlman, M.D., M.P.H. | October 1, 2010 |
| Clinical Team Leader | Date |

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALMA C DAVIDSON
10/01/2010

JANICE K POHLMAN
11/01/2010