SAMSON®
MEDICAL TECHNOLOGIES, L.L.C.

June 12, 2003

3995 '03 JUN 23 P5:38

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

CITIZEN'S PETITION

The undersigned submits this petition pursuant to 21 CFR 314.93 to request that the Commissioner of Food and Drug permit the filing of an Abbreviated New Drug Application for a drug that has the same active ingredient and dosage form listed in FDA's publication entitled, *Approved Drug Products with Therapeutic Equivalence Evaluations*, current Internet edition, but differs in its dosage strength (total quantity of active ingredient in the package).

A. Action Requested

By this petition, we hereby request the Agency to permit the filing of an Abbreviated New Drug Application for a Ceftazidime for Injection, USP, pharmacy bulk package in a 100 gram dosage strength packaged in plastic bags that are contained within foil outer wraps. This drug differs from the reference listed drug, Glaxo Smith Kline Fortaz® (Ceftazidime for Injection, USP), 6 gram, Pharmacy Bulk Package, in its total dosage strength but not the dosage amount recommended for administration to the patient.

B. Statement of Grounds

In accordance with section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, a petition may be filed, with the Agency, seeking permission to file an Abbreviated New Drug Application for a new drug, which differs from a "listed" drug in dosage strength.

P.O. Box 2730, Cherry Hill, NJ 08034 • 2050 Springdale Road, Suite 400, Cherry Hill, NJ 08003
Toll-Free: (877) 418-3600 • Phone: (856) 751-5051 • Fax: (856) 751-5044
Email: SAMSONMEDTEK@aol.com • www.samsonmt.com

2003P-0292

CP1

The Act stipulates that such a petition must be approved by the Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product.

The reference listed drug product, Glaxo Smith Kline Fortaz® (Ceftazidime for Injection, USP), 6 gram Pharmacy Bulk Package, is identified in the Prescription Product List of the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) as supplied in the CDER Internet home page. A printout of this listing by active ingredient detail is provided in Exhibit A.

We propose to develop a pharmacy bulk package of Ceftazidime for Injection, USP, in a 100 gram dosage strength packaged in plastic bags that are contained within secondary foil outer wraps. The inner (product) bag is provided with an injection port to allow aseptic constitution of the solution and transfer into dispensing units. The same formulation and route of administration as the reference listed drug Pharmacy Bulk Package are proposed, i.e., Ceftazidime for Injection, USP, for intravenous injection after constitution with the specified diluent, Sterile Water for Injection. The proposed product will be administered at the same dosage recommendations as the listed drug and is expected to have the same therapeutic effect when administered for use as indicated in the product labeling.

Labeling for the reference listed drug, Glaxo Smith Kline Fortaz® (Ceftazidime for Injection, USP), 6 gram Pharmacy Bulk Package, is included in Exhibit B. Labeling for the proposed product is expected to be substantially the same as the sections pertaining to the pharmacy bulk package dosage form of the listed drug labeling, with the exception that reference to Glaxo Smith Kline Fortaz® (Ceftazidime for Injection, USP), 6 gram Pharmacy Bulk Package will be replaced with "Ceftazidine for Injection, USP, 100 gram Pharmacy Bulk Package," and references to other dosage forms will be eliminated. A copy of the proposed draft package insert is provided in Exhibit C.

The proposed strength is designed to be used by hospital pharmacies or centralized compounding pharmacies that provide hospitals, organized into networks, with a standard platform of the prepared formulation reconstituted to the required concentration and filled into syringes for intravenous delivery of medication. The benefit of this dosage strength is the optimization of drug therapy and delivery of hospital pharmacy services. This new dosage strength enhances aseptic control, since product constitution takes place within a closed system design, and disposable components are used. Reduced handling of the product, with one bag equivalent to 16.66 vials of the listed drug, further ensures that sterility of the product is maintained during constitution and filling into syringes. This proposed bag system configuration is particularly well adapted for use in the hospital or compounding pharmacy.

Thus, the use of the 100 gram pharmacy bulk packages of Ceftazidime for Injection, USP, in the double plastic and foil bag container, will not only increase efficiency at the hospital or compounding pharmacy level, but it will also permit minimal handling of the product that will result in improved quality assurance.

Introduction of the double bag container will not have an impact on the established safety and efficacy of Ceftazidime for Injection, USP, and since the product is an injectable preparation to be administered at the same strength as the listed drug, a bioequivalence study is not viewed as a requirement.

C. Environmental Impact

An environmental impact analysis report is not required for this petition per 21 CFR 25.24.

D. Economic Impact

This information will be provided upon request from the Agency.

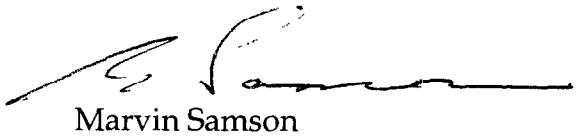
E. Certification

The undersigned certifies that, to the best knowledge of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

If you have any questions or need additional information, please feel free to contact me.

Sincerely,

SAMSON MEDICAL TECHNOLOGIES, L.L.C.



Marvin Samson
Chief Executive Officer

Enclosures: Exhibits A, B and C

EXHIBIT A

Electronic Orange Book Pages Showing
the Listing of the Listed Drug:
Glaxo Smith Kline's Fortaz®

Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

Current through April 2003

Preface

FAQ

Search by Active Ingredient **Search by Applicant Holder**

Search by Proprietary Name **Search by Application Number**

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

Updated: May 29, 2003

Active Ingredient Search Results from "Rx" table for query on "ceftazidime."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietar Name
062662	AP	No	CEFTAZIDIME	Injectable; Injection	1GM/VIAL	TAZICEF
064032	AP	No	CEFTAZIDIME	Injectable; Injection	1GM/VIAL	TAZICEF
064032	AP	No	CEFTAZIDIME	Injectable; Injection	2GM/VIAL	TAZICEF
062662	AP	No	CEFTAZIDIME	Injectable; Injection	2GM/VIAL	TAZICEF
062662	AP	No	CEFTAZIDIME	Injectable; Injection	500MG/VIAL	TAZICEF
062662	AP	No	CEFTAZIDIME	Injectable; Injection	6GM/VIAL	TAZICEF
050578	AP	Yes	CEFTAZIDIME	Injectable; Injection	1GM/VIAL	FORTAZ
050578	AP	Yes	CEFTAZIDIME	Injectable; Injection	2GM/VIAL	FORTAZ
050578	AP	Yes	CEFTAZIDIME	Injectable; Injection	500MG/VIAL	FORTAZ
050578	AP	Yes	CEFTAZIDIME	Injectable; Injection	6GM/VIAL	FORTAZ
062640	AP	No	CEFTAZIDIME	Injectable; Injection	1GM/VIAL	TAZIDIME
062655	AP	No	CEFTAZIDIME	Injectable; Injection	1GM/VIAL	TAZIDIME
062655	AP	No	CEFTAZIDIME	Injectable; Injection	2GM/VIAL	TAZIDIME
062640	AP	No	CEFTAZIDIME	Injectable; Injection	2GM/VIAL	TAZIDIME
062640	AP	No	CEFTAZIDIME	Injectable;	500MG/VIAL	TAZIDIME

				Injection		
050646		Yes	CEFTAZIDIME (ARGININE FORMULATION)	Injectable; Injection	10GM/VIAL	CEPTAZ
050646		Yes	CEFTAZIDIME (ARGININE FORMULATION)	Injectable; Injection	1GM/VIAL	CEPTAZ
050646		Yes	CEFTAZIDIME (ARGININE FORMULATION)	Injectable; Injection	2GM/VIAL	CEPTAZ
063221		Yes	CEFTAZIDIME SODIUM	Injectable; Injection	EQ 10MG BASE/ML	CEFTAZIDIM SODIUM IN PLASTIC CONTAINER
063221	AP	No	CEFTAZIDIME SODIUM	Injectable; Injection	EQ 20MG BASE/ML	CEFTAZIDIM SODIUM IN PLASTIC CONTAINER
063221	AP	No	CEFTAZIDIME SODIUM	Injectable; Injection	EQ 40MG BASE/ML	CEFTAZIDIM SODIUM IN PLASTIC CONTAINER
050634	AP	Yes	CEFTAZIDIME SODIUM	Injectable; Injection	EQ 20MG BASE/ML	FORTAZ IN PLASTIC CONTAINER
050634	AP	Yes	CEFTAZIDIME SODIUM	Injectable; Injection	EQ 40MG BASE/ML	FORTAZ IN PLASTIC CONTAINER

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

Search results from the "Rx" table for query on "050578."

Active Ingredient:	CEFTAZIDIME
Dosage Form;Route:	Injectable; Injection
Proprietary Name:	FORTAZ
Applicant:	GLAXOSMITHKLINE
Strength:	500MG/VIAL
Application Number:	050578
Product Number:	001
Approval Date:	JUL 19, 1985
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	CEFTAZIDIME
Dosage Form;Route:	Injectable; Injection
Proprietary Name:	FORTAZ
Applicant:	GLAXOSMITHKLINE
Strength:	1GM/VIAL
Application Number:	050578
Product Number:	002
Approval Date:	JUL 19, 1985
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	CEFTAZIDIME
Dosage Form;Route:	Injectable; Injection
Proprietary Name:	FORTAZ
Applicant:	GLAXOSMITHKLINE
Strength:	2GM/VIAL

Application Number:	050578
Product Number:	003
Approval Date:	JUL 19, 1985
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	CEFTAZIDIME
Dosage Form;Route:	Injectable; Injection
Proprietary Name:	FORTAZ
Applicant:	GLAXOSMITHKLINE
Strength:	6GM/VIAL
Application Number:	050578
Product Number:	004
Approval Date:	JUL 19, 1985
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

Thank you for searching the Electronic Orange Book!

Return to Electronic Orange Book Home Page

EXHIBIT B

Copy of the Package Insert
for the Listed Drug:
Glaxo Smith Kline's Fortaz®

PRESCRIBING INFORMATION

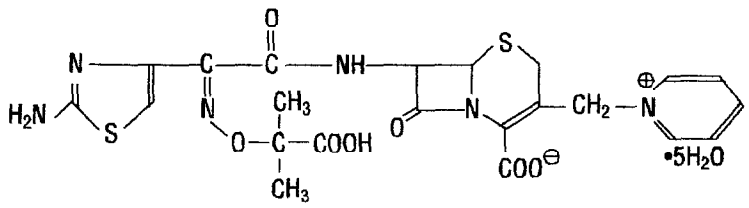
FORTAZ®
(ceftazidime for injection)

FORTAZ®
(ceftazidime sodium injection)

For Intravenous or Intramuscular Use

DESCRIPTION

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]]. It has the following structure:



The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.

FORTAZ is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. The 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.

FORTAZ in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-Vantage® vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of FORTAZ range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8.

FORTAZ is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of dextrose hydrous, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed FORTAZ range in color from light yellow to amber. The solution is intended for intravenous (IV) use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of thawed solutions ranges from 5 to 7.5.

The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040. Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

After IV administration of 500-mg and 1-g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500-mg, 1-g, and 2-g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500-mg, 1-g, and 2-g doses to these volunteers over an 8-hour interval are given in Table 1.

Table 1. Average Serum Concentrations of Ceftazidime

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 hr	1 hr	2 hr	4 hr	8 hr
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

Following intramuscular (IM) administration of 500-mg and 1-g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 and 39 mcg/mL, respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the IM administration of 500-mg and 1-g doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the IV administration of single 500-mg or 1-g doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine.

The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage adjustments in such patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.

Table 2. Ceftazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0-2 hr	2,100.0
	2 g IV	6	0-2 hr	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 hr	25.6
Peritoneal fluid	2 g IV	8	2 hr	48.6
Sputum	1 g IV	8	1 hr	9.0
Cerebrospinal fluid	2 g q8hr IV	5	120 min	9.8
(inflamed meninges)	2 g q8hr IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 hr	11.0
Blister fluid	1 g IV	7	2-3 hr	19.7
Lymphatic fluid	1 g IV	7	2-3 hr	23.4
Bone	2 g IV	8	0.67 hr	31.1
Heart muscle	2 g IV	35	30-280 min	12.7
Skin	2 g IV	22	30-180 min	6.6
Skeletal muscle	2 g IV	35	30-280 min	9.4
Myometrium	2 g IV	31	1-2 hr	18.7

Microbiology: Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to ceftazidime in vitro, including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime has been shown to be active against the following organisms both in vitro and in clinical infections (see INDICATIONS AND USAGE).

Aerobes, Gram-negative: *Citrobacter* spp., including *Citrobacter freundii* and *Citrobacter diversus*; *Enterobacter* spp., including *Enterobacter cloacae* and *Enterobacter aerogenes*; *Escherichia coli*; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp. (including *Klebsiella pneumoniae*); *Neisseria meningitidis*; *Proteus mirabilis*; *Proteus vulgaris*; *Pseudomonas* spp. (including *Pseudomonas aeruginosa*); and *Serratia* spp.

Aerobes, Gram-positive: *Staphylococcus aureus*, including penicillinase- and non–penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci); *Streptococcus pneumoniae*; and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Anaerobes: *Bacteroides* spp. (NOTE: many strains of *Bacteroides fragilis* are resistant).

Ceftazidime has been shown to be active in vitro against most strains of the following organisms; however, the clinical significance of these data is unknown: *Acinetobacter* spp., *Clostridium* spp. (not including *Clostridium difficile*), *Haemophilus parainfluenzae*, *Morganella morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae*, *Peptococcus* spp.,

Peptostreptococcus spp., *Providencia* spp. (including *Providencia rettgeri*, formerly *Proteus rettgeri*), *Salmonella* spp., *Shigella* spp., *Staphylococcus epidermidis*, and *Yersinia enterocolitica.*

Ceftazidime and the aminoglycosides have been shown to be synergistic in vitro against *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been shown to be synergistic in vitro against *Pseudomonas aeruginosa.*

Ceftazidime is not active in vitro against methicillin-resistant staphylococci, *Streptococcus faecalis* and many other enterococci, *Listeria monocytogenes*, *Campylobacter* spp., or *Clostridium difficile.*

Susceptibility Tests: *Diffusion Techniques:* Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg ceftazidime disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 15 to 17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by in vitro tests to be active against certain strains found resistant when other beta-lactam disks are used.

Standardized procedures require the use of laboratory control organisms. The 30-mcg ceftazidime disk should give zone diameters between 25 and 32 mm for *Escherichia coli* ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be between 22 and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be between 16 and 20 mm.

Dilution Techniques: In other susceptibility testing procedures, e.g., ICS agar dilution or the equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are considered resistant to ceftazidime if the MIC is ≥64 mcg/mL. Organisms having an MIC value of <64 mcg/mL but >16 mcg/mL are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftazidime powder should give MIC values in the range of 4 to 16 mcg/mL for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range should be between 0.125 and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC range should be between 0.5 and 2 mcg/mL.

INDICATIONS AND USAGE

FORTAZ is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia*

coli; *Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae*; and *Staphylococcus aureus* (methicillin-susceptible strains).

2. **Skin and Skin-Structure Infections** caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).
3. **Urinary Tract Infections,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa*; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Klebsiella* spp.; and *Escherichia coli.*
4. **Bacterial Septicemia** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Haemophilus influenzae, Escherichia coli*, *Serratia* spp., *Streptococcus pneumoniae,* and *Staphylococcus aureus* (methicillin-susceptible strains).
5. **Bone and Joint Infections** caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible strains).
6. **Gynecologic Infections,** including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli.*
7. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
8. **Central Nervous System Infections,** including meningitis, caused by *Haemophilus influenzae* and *Neisseria meningitidis*. Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

Specimens for bacterial cultures should be obtained before therapy in order to isolate and identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

FORTAZ may be used alone in cases of confirmed or suspected sepsis. Ceftazidime has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used.

FORTAZ may also be used concomitantly with other antibiotics, such as aminoglycosides, vancomycin, and clindamycin; in severe and life-threatening infections; and in the immunocompromised patient. When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.

CONTRAINDICATIONS

FORTAZ is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH FORTAZ IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE

PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO FORTAZ OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftazidime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see PRECAUTIONS).

PRECAUTIONS

General: High and prolonged serum ceftazidime concentrations can occur from usual dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these patients can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

As with other antibiotics, prolonged use of FORTAZ may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Inducible type I beta-lactamase resistance has been noted with some organisms (e.g., *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

FORTAZ should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on in vitro studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism in vivo, particularly when bactericidal activity is desired, this drug combination should be avoided.

Drug/Laboratory Test Interactions: The administration of ceftazidime may result in a false-positive reaction for glucose in the urine when using CLINITEST® tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) be used.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an Ames test were both negative for mutagenic effects.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to FORTAZ. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when FORTAZ is administered to a nursing woman.

Pediatric Use: (see DOSAGE AND ADMINISTRATION).

Geriatric Use: Of the 2,221 subjects who received ceftazidime in 11 clinical studies, 824 (37%) were 65 and over while 391 (18%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiramlike reactions were reported.

The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects, reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Hypersensitivity Reactions, reported in 2% of patients, were pruritus, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms, reported in fewer than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Central Nervous System Reactions (fewer than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported in renally impaired patients treated with unadjusted dosing regimens of ceftazidime (see PRECAUTIONS: General).

Less Frequent Adverse Events (fewer than 1%) were candidiasis (including oral thrush) and vaginitis.

Hematologic: Rare cases of hemolytic anemia have been reported.

Laboratory Test Changes noted during clinical trials with FORTAZ were transient and included: eosinophilia (1 in 13), positive Coombs test without hemolysis (1 in 23), thrombocytosis (1 in 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19), and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very rarely.

POSTMARKETING EXPERIENCE WITH FORTAZ PRODUCTS

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.**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.

Cephalosporin-Class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Colitis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose, pancytopenia.

OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body.

DOSAGE AND ADMINISTRATION

Dosage: The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The guidelines for dosage of FORTAZ are listed in Table 3. The following dosage schedule is recommended.

Table 3. Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dosage	**1 gram IV or IM**	**q8-12hr**
Uncomplicated urinary tract infections	250 mg IV or IM	q12hr
Bone and joint infections	2 grams IV	q12hr
Complicated urinary tract infections	500 mg IV or IM	q8-12hr
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 gram IV or IM	q8hr
Serious gynecologic and intra-abdominal infections	2 grams IV	q8hr
Meningitis	2 grams IV	q8hr
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8hr
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 grams per day	q8hr
Neonates (0-4 weeks)	30 mg/kg IV	q12hr
Infants and children (1 month-12 years)	30-50 mg/kg IV to a maximum of 6 grams per day†	q8hr

*Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.

† The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

Impaired Hepatic Function: No adjustment in dosage is required for patients with hepatic dysfunction.

Impaired Renal Function: Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] <50 mL/min), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of

1 gram of FORTAZ may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in Table 4.

Table 4. Recommended Maintenance Dosages of FORTAZ in Renal Insufficiency
NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.

Creatinine Clearance (mL/min)	Recommended Unit Dose of FORTAZ	Frequency of Dosing
50-31	1 gram	q12hr
30-16	1 gram	q24hr
15-6	500 mg	q24hr
<5	500 mg	q48hr

When only serum creatinine is available, the following formula (Cockcroft's equation)[4] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x male value

In patients with severe infections who would normally receive 6 grams of FORTAZ daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency may be increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period.

FORTAZ can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of FORTAZ may be given, followed by 500 mg every 24 hours. In addition to IV use, FORTAZ can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

Note: Generally FORTAZ should be continued for 2 days after the signs and symptoms of infection have disappeared, but in complicated infections longer therapy may be required.

Administration: FORTAZ may be given intravenously or by deep IM injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. Intra-arterial administration should be avoided (see PRECAUTIONS).

Intramuscular Administration: For IM administration, FORTAZ should be constituted with one of the following diluents: Sterile Water for Injection, Bacteriostatic Water for Injection, or 0.5% or 1% Lidocaine Hydrochloride Injection. Refer to Table 5.

Intravenous Administration: The IV route is preferable for patients with bacterial septicemia, bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating

conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or pending.

For direct intermittent IV administration, constitute FORTAZ as directed in Table 5 with Sterile Water for Injection. Slowly inject directly into the vein over a period of 3 to 5 minutes or give through the tubing of an administration set while the patient is also receiving one of the compatible IV fluids (see COMPATIBILITY AND STABILITY).

For IV infusion, constitute the 1- or 2-gram infusion pack with 100 mL of Sterile Water for Injection or one of the compatible IV fluids listed under the COMPATIBILITY AND STABILITY section. Alternatively, constitute the 500-mg, 1-gram, or 2-gram vial and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids.

Intermittent IV infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable to discontinue the other solution.

ADD-Vantage vials are to be constituted only with 50 or 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection in Abbott ADD-Vantage flexible diluent containers (see Instructions for Constitution). ADD-Vantage vials that have been joined to Abbott ADD-Vantage diluent containers and activated to dissolve the drug are stable for 24 hours at room temperature or for 7 days under refrigeration. Joined vials that have not been activated may be used within a 14-day period; this period corresponds to that for use of Abbott ADD-Vantage containers following removal of the outer packaging (overwrap).

Freezing solutions of FORTAZ in the ADD-Vantage system is not recommended.

Table 5. Preparation of Solutions of FORTAZ

Size	Amount of Diluent to be Added (mL)	Approximate Available Volume (mL)	Approximate Ceftazidime Concentration (mg/mL)
Intramuscular			
500-mg vial	1.5	1.8	280
1-gram vial	3.0	3.6	280
Intravenous			
500-mg vial	5.0	5.3	100
1-gram vial	10.0	10.6	100
2-gram vial	10.0	11.5	170
Infusion pack			
1-gram vial	100*	100	10
2-gram vial	100*	100	20
Pharmacy bulk package			
6-gram vial	26	30	200

*Note: Addition should be in 2 stages (see Instructions for Constitution).

All vials of FORTAZ as supplied are under reduced pressure. When FORTAZ is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use please follow the recommended techniques of constitution described on the detachable Instructions for Constitution section of this insert.

Solutions of FORTAZ, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with FORTAZ and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Directions for Use of FORTAZ Frozen in GALAXY® Plastic Containers: FORTAZ supplied as a frozen, sterile, iso-osmotic, nonpyrogenic solution in plastic containers is to be administered after thawing either as a continuous or intermittent IV infusion. The thawed solution is stable for 24 hours at room temperature or for 7 days if stored under refrigeration. **Do not refreeze.**

Thaw container at room temperature (25°C) or under refrigeration (5°C). Do not force thaw by immersion in water baths or by microwave irradiation. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Mix after solution has reached room temperature. Check for minute leaks by squeezing bag firmly. Discard bag if leaks are found as sterility may be impaired. Do not add supplementary medication. Do not use unless solution is clear and seal is intact.

Use sterile equipment.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

COMPATIBILITY AND STABILITY

Intramuscular: FORTAZ, when constituted as directed with Sterile Water for Injection, Bacteriostatic Water for Injection, or 0.5% or 1% Lidocaine Hydrochloride Injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions in Sterile Water for Injection that are frozen immediately after constitution in the original container are stable for 3 months when stored at -20°C. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator.

Intravenous: FORTAZ, when constituted as directed with Sterile Water for Injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions in Sterile Water for Injection in the infusion vial or in 0.9% Sodium Chloride Injection in VIAFLEX® small-volume containers that are frozen immediately after constitution are stable for 6 months when stored at -20°C. Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 24 hours at room temperature or for 7 days in a refrigerator. More concentrated solutions in Sterile Water for Injection in the original container that are frozen immediately after constitution are stable for 3 months when stored at -20°C. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator.

FORTAZ is compatible with the more commonly used IV infusion fluids. Solutions at concentrations between 1 and 40 mg/mL in 0.9% Sodium Chloride Injection; 1/6 M Sodium

Lactate Injection; 5% Dextrose Injection; 5% Dextrose and 0.225% Sodium Chloride Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride Injection; 10% Dextrose Injection; Ringer's Injection, USP; Lactated Ringer's Injection, USP; 10% Invert Sugar in Water for Injection; and NORMOSOL®-M in 5% Dextrose Injection may be stored for up to 24 hours at room temperature or for 7 days if refrigerated.

The 1- and 2-g FORTAZ ADD-Vantage vials, when diluted in 50 or 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection, may be stored for up to 24 hours at room temperature or for 7 days under refrigeration.

FORTAZ is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not recommended as a diluent. Solutions of FORTAZ in 5% Dextrose Injection and 0.9% Sodium Chloride Injection are stable for at least 6 hours at room temperature in plastic tubing, drip chambers, and volume control devices of common IV infusion sets.

Ceftazidime at a concentration of 4 mg/mL has been found compatible for 24 hours at room temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose Injection when admixed with: cefuroxime sodium (ZINACEF®) 3 mg/mL; heparin 10 or 50 U/mL; or potassium chloride 10 or 40 mEq/L.

Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines (with 1 of the compatible IV fluids) between the administration of these 2 agents.

Note: Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit.

As with other cephalosporins, FORTAZ powder as well as solutions tend to darken, depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

HOW SUPPLIED

FORTAZ in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. FORTAZ is a dry, white to off-white powder supplied in vials and infusion packs as follows:

NDC 0173-0377-31 500-mg* Vial (Tray of 25)
NDC 0173-0378-35 1-g* Vial (Tray of 25)
NDC 0173-0379-34 2-g* Vial (Tray of 10)
NDC 0173-0380-32 1-g* Infusion Pack (Tray of 10)
NDC 0173-0381-32 2-g* Infusion Pack (Tray of 10)
NDC 0173-0382-37 6-g* Pharmacy Bulk Package (Tray of 6)
NDC 0173-0434-00 1-g ADD-Vantage® Vial (Tray of 25)
NDC 0173-0435-00 2-g ADD-Vantage® Vial (Tray of 10)
(The above ADD-Vantage vials are to be used only with Abbott ADD-Vantage diluent containers.)

FORTAZ frozen as a premixed solution of ceftazidime sodium should not be stored above -20°C. FORTAZ is supplied frozen in 50-mL, single-dose, plastic containers as follows:

NDC 0173-0412-00 1-g* Plastic Container (Carton of 24)
NDC 0173-0413-00 2-g* Plastic Container (Carton of 24)
*Equivalent to anhydrous ceftazidime.

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol.* 1966;45:493-496.
2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disc Susceptibility Tests.* (M2-A3). December 1984.
3. Certification procedure for antibiotic sensitivity discs (21 CFR 460.1). *Federal Register.* May 30, 1974;39:19182-19184.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

GlaxoSmithKline
FORTAZ® (ceftazidime for injection):
GlaxoSmithKline
Research Triangle Park, NC 27709

FORTAZ® (ceftazidime sodium injection):
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
by Baxter Healthcare Corporation,
Deerfield, IL 60015

April 2002 RL-1090

TEAR AWAY

FORTAZ®
(ceftazidime for injection)

Instructions for Constitution

Vials: 500 mg IM/IV, 1 g IM/IV, 2 g IV

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution will be obtained in 1 to 2 minutes.
3. Invert the vial. Ensuring that the syringe plunger is fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the headspace. The withdrawn solution may contain some bubbles of carbon dioxide.

Note: As with the administration of all parenteral products, accumulated gases should be expressed from the syringe immediately before injection of FORTAZ.

Infusion Pack: 1 g, 2 g

1. Insert the syringe needle through the vial closure and inject 10 mL of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution will be obtained in 1 to 2 minutes.
3. Insert a gas-relief needle through the vial closure to relieve the internal pressure. With the gas-relief needle in position, add the remaining 90 mL of diluent. Remove the gas-relief needle and syringe needle; shake the vial and set up for infusion in the normal way.

Note: To preserve product sterility, it is important that a gas-relief needle is *not* inserted through the vial closure before the product has dissolved.

ADD-Vantage® Vials: 1 g, 2 g

To Open Diluent Container:
Peel the corner of the ADD-Vantage diluent overwrap and remove flexible diluent container. Some opacity of the plastic flexible container due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container (Use Aseptic Technique):
1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see Figure 1), then pull straight up to remove the cap (see Figure 2).
Note: Once the breakaway cap has been removed, do not access vial with syringe.

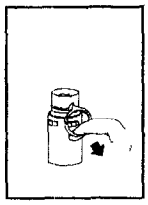


Figure 1

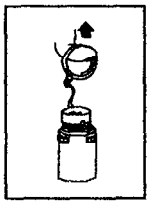


Figure 2

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover (see Figure 3).

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately one-half turn (180°) after the first audible click (see Figure 4). The clicking sound does not assure a seal; the vial must be turned as far as it will go.
Note: Once vial is seated, do not attempt to remove (see Figure 4).

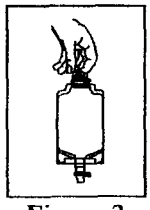


Figure 3

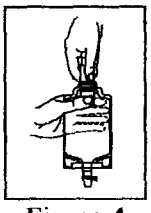
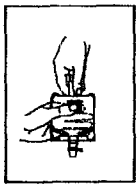


Figure 4

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container, telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container (see Figure 5).
3. Pull the inner cap from the drug vial (see Figure 6). Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.



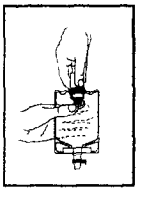


Figure 5 Figure 6

4. Mix container contents thoroughly and use within the specified time.

Preparation for Administration (Use Aseptic Technique):

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
   Note: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

Pharmacy Bulk Package: 6 g

1. Insert the syringe needle through the vial closure and inject 26 mL of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution containing approximately 1 g of ceftazidime activity per 5 mL will be obtained in 1 to 2 minutes.
3. Insert a gas-relief needle through the vial closure to relieve the internal pressure. Remove the gas-relief needle before extracting any solution.

Note: To preserve product sterility, it is important that a gas-relief needle is *not* inserted through the vial closure before the product has dissolved.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

April 2002 RL-1090

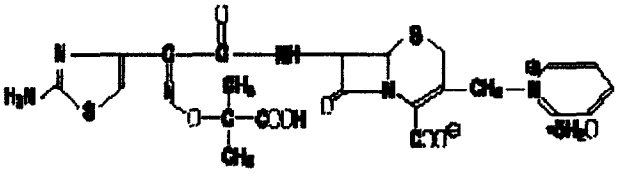
EXHIBIT C

Copy of the Proposed Draft Package Insert for
Ceftazidime for Injection, USP

CEFTAZIDIME FOR INJECTION, USP

DESCRIPTION

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-], hydroxide, inner salt, [6R-[6α,7β(Z)]]. It has the following structure:



The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.

Ceftazidime for Injection, USP is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. The 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.

Ceftazidime for Injection, USP, in sterile crystalline form, is supplied in a Pharmacy Bulk Package consisting of a plastic bag contained within a foil outer wrap. The inner bag is provided with an injection port to allow introduction of the diluent inside the bag for constituting the solution and for transfer of the constituted solution into syringes for product administration. Each bag contains the equivalent of 100 grams of anhydrous ceftazidime. Solutions of Ceftazidime for Injection, USP range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8.

CLINICAL PHARMACOLOGY

After IV administration of 500 mg and 1 g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500 mg, 1 g, and 2 g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500 mg, 1 g, and 2 g doses to these volunteers over an 8-hour interval are given in Table 1.

Table 1. Average Serum Concentration of Ceftazidime

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 hr	1 hr	2 hr	4 hr	8 hr
500 mg	42	25	12	6	2
1 gram	60	39	23	11	3
2 grams	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

Following intramuscular (IM) administration of 500 mg and 1 g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 and 39 mcg/mL, respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the IM administration of 500 mg and 1 g doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the IV administration of single 500 mg or 1 g doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine.

The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage

adjustments in such patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.

Table 2. Ceftazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0-2 hr	2,100.0
	2 g IV	6	0-2 hr	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 hr	25.6
Peritoneal fluid	2 g IV	8	2 hr	48.6
Sputum	1 g IV	8	1 hr	9.0
Cerebrospinal fluid	2 g q8hr IV	5	120 min	9.8
(inflamed meninges)	2 g q8hr IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 hr	11.0
Blister fluid	1 g IV	7	2-3 hr	19.7
Lymphatic fluid	1 g IV	7	2-3 hr	23.4
Bone	2 g IV	8	0.67 hr	31.1
Heart muscle	2 g IV	35	30-280 min	12.7
Skin	2 g IV	22	30-180 min	6.6
Skeletal muscle	2 g IV	35	30-280 min	9.4
Myometrium	2 g IV	31	1-2 hr	18.7

Microbiology: Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to ceftazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime has been shown to be active against the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Aerobes, Gram-negative: *Citrobacter* spp., including *Citrobacter freundii* and *Citrobacter diversus*; *Enterobacter* spp., including *Enterobacter cloacae* and *Enterobacter aerogenes*; *Escherichia coli*; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp. (including *Klebsiella pneumoniae*); *Neisseria meningitidis*; *Proteus mirabilis*; *Proteus vulgaris*; *Pseudomonas* spp. (including *Pseudomonas aeruginosa*); and *Serratia* spp.

Aerobes, Gram-positive: *Staphylococcus aureus,* including penicillinase- and non-penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci); *Streptococcus pneumoniae;* and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Anaerobes: *Bacteroides* spp. (NOTE: many strains of *Bacteroides fragilis* are resistant).

Ceftazidime has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown: *Acinetobacter* spp., *Clostridium* spp. (not including *Clostridium difficile*), *Haemophilus parainfluenzae, Morganella morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae, Peptococcus* spp., *Peptostreptococcus* spp., *Providencia* spp. (including *Providencia rettgeri,* formerly *Proteus rettgeri*), *Salmonella* spp., *Shigella* spp., *Staphylococcus epidermidis,* and *Yersinia enterocolitica.*

Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa.*

Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus faecalis* and many other enterococci, *Listeria monocytogenes, Campylobacter* spp., or *Clostridium difficile.*

Susceptibility Tests: ***Diffusion Techniques***: Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg ceftazidime disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 15 to 17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.

Standardized procedures require the use of laboratory control organisms. The 30 mcg ceftazidime disk should give zone diameters between 25 and 32 mm for *Escherichia coli* ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be between 22 and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be between 16 and 20 mm.

Dilution Techniques: In other susceptibility testing procedures, e.g., ICS agar dilution or the equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are considered resistant to ceftazidime if the MIC is $\geq$ 64 mcg/mL. Organisms having an MIC value of $<$ 64 mcg/mL but $>$ 16 mcg/mL are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftazidime powder should give MIC values in the range of 4 to 16 mcg/mL for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range should be between 0.125 and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC range should be between 0.5 and 2 mcg/mL.

INDICATIONS AND USAGE

Ceftazidime for Injection, USP is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae,* including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis; Escherichia coli; Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae;* and *Staphylococcus aureus* (methicillin-susceptible strains).

2. **Skin and Skin-Structure Infections** caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *Escherichia coli; Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus; Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

3. **Urinary Tract Infections,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa; Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus; Klebsiella* spp.; and *Escherichia coli.*

4. **Bacterial Septicemia** caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Haemophilus influenzae, Escherichia coli, Serratia* spp., *Streptococcus pneumoniae,* and *Staphylococcus aureus* (methicillin-susceptible strains).

5. **Bone and Joint Infections** caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible strains).

6. **Gynecologic Infections,** including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli.*

7. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).

8. **Central Nervous System Infections,** including meningitis, caused by *Haemophilus influenzae* and *Neisseria meningitidis.* Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

Specimens for bacterial cultures should be obtained before therapy in order to isolate and identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

Ceftazidime for Injection, USP may be used alone in cases of confirmed or suspected sepsis. Ceftazidime has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used.

Ceftazidime for Injection may also be used concomitantly with other antibiotics, such as aminoglycosides, vancomycin, and clindamycin; in severe and life-threatening infections; and in the immunocompromised patient. When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.

CONTRAINDICATIONS

Ceftazidime for Injection, USP is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFTAZIDIME FOR INJECTION, USP IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLEGY. IF AN ALLERGIC REACTION TO CEFTAZIDIME FOR INJECTION, USP OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftazidime, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see PRECAUTIONS).

PRECAUTIONS

General: High and prolonged serum ceftazidime concentrations can occur from usual dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these patients can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia.

Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

As with other antibiotics, prolonged use of Ceftazidime for Injection, USP may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Inducible type I beta-lactamase resistance has been noted with some organisms (e.g., *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.) As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Ceftazidime for Injection, USP should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism *in vivo*, particularly when bactericidal activity is desired, this drug combination should be avoided.

Drug/Laboratory Test Interactions: The administration of ceftazidime may result in a false-positive reaction for glucose in the urine when using CLINITEST® tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) be used.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an Ames test were both negative for mutagenic effects.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceftazidime for Injection, USP. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when Ceftazidime for Injection, USP is administered to a nursing woman.

Pediatric Use: (see DOSAGE AND ADMINISTRATION).

Geriatric Use: Of the 2,221 subjects who received ceftazidime in 11 clinical studies, 824 (37%) were 65 and over while 391 (18%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiramlike reactions were reported.

The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects, reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Hypersensitivity Reactions, reported in 2%, of patients, were pruritus, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285

patients. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms, reported in fewer than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Central Nervous System Reactions (fewer than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported in renally impaired patients treated with unadjusted dosing regimens of ceftazidime (see PRECAUTIONS: General).

Less Frequent Adverse Events (fewer than 1%) were candidiasis (including oral thrush) and vaginitis.

Hematologic: Rare cases of hemolytic anemia have been reported.

Laboratory Test Changes noted during clinical trials with Ceftazidime for Injection, USP were transient and included: eosinophilia (1 in 13), positive Coombs test without hemolysis (1 in 23), thrombocytosis (1 in 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19), and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very rarely.

POSTMARKETING EXPERIENCE WITH CEFTAZIDIME FOR INJECTION, USP PRODUCTS

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

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.

Cephalosporin-Class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Colitis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose, pancytopenia.

OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body.

DOSAGE AND ADMINISTRATION

Dosage: The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The guidelines for dosage of Ceftazidime for Injection, USP are listed in Table 3. The following dosage schedule is recommended.

Table 3. Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dosage	**1 gram IV or IM**	**q8-12hr**
Uncomplicated urinary tract infections	250 mg IV or IM	q12hr
Bone and joint infections	2 grams IV	q12hr
Complicated urinary tract infections	500 mg IV or IM	q8-12hr
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 gram IV or IM	q8hr
Serious gynecologic and intra-abdominal infections	2 grams IV	q8hr
Meningitis	2 grams IV	q8hr
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8hr
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 grams per day	q8hr
Neonates (0-4 weeks)	30 mg/kg IV	q12hr
Infants and children (1 month-12 years)	30-50 mg/kg IV to a maximum of 6 grams per day†	q8hr

*Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.

† The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

Impaired Hepatic Function: No adjustment in dosage is required for patients with hepatic dysfunction.

Impaired Renal Function: Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] < 50 mL/min), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 gram of Ceftazidime for Injection, USP may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in Table 4.

Table 4. Recommended Maintenance Dosages of Ceftazidime for Injection, USP in Renal Insufficiency

NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.

Creatinine Clearance (mL/min)	Recommended Unit Dose of Ceftazidime for Injection, USP	Frequency of Dosing
50-31	1 gram	q12hr
30-16	1 gram	q24hr
15-6	500 mg	q24hr
< 5	500 mg	q48hr

When only serum creatinine is available, the following formula (Cockcroft's equation)[4] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x male value

In patients with severe infections who would normally receive 6 grams of Ceftazidime for Injection, USP daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency may be increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of infection, and susceptibility of the causative organism.

In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period.

Ceftazidime for Injection, USP can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of Ceftazidime for Injection, USP may be given, followed by 500 mg every 24 hours. In addition to IV use, Ceftazidime for Injection, USP can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

Note: Generally, Ceftazidime for Injection, USP should be continued for 2 days after the signs and symptoms of infection have disappeared, but in complicated infections longer therapy may be required.

Administration: Ceftazidime for Injection, USP may be given intravenously or by deep IM injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. Intra-arterial administration should be avoided (see PRECAUTIONS).

Intravenous Administration: The IV route is preferable for patients with bacterial septicemia, bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or pending.

For IV administration, constitute Ceftazidime for Injection, USP as directed in Table 5 with Sterile Water for Injection.

Table 5. Preparation of Solutions of Ceftazidime for Injection, USP

Size	Amount of Diluent to be Added (mL)	Approximate Available Volume (mL)	Approximate Ceftazidime Concentration (mg/mL)
100 gram SmartPak® bag	433	500	200
	933	1,000	100

The 100 gram SmartPak® bags should be constituted with 433 mL of Sterile Water for Injection, USP to yield a final concentration of 200 mg/mL or 933 mL of Sterile Water for Injection, USP to yield a final concentration of 100 mg/mL.

CAUTION: THE 100 GRAM SMARTPAK® BAGS ARE NOT INTENDED FOR DIRECT INFUSION. The SmartPak® package is for use in a pharmacy admixture service only under a laminar flow hood. Entry into the bag must be made with a sterile transfer set or other sterile dispensing device, and the contents dispensed in aliquots using aseptic technique. The use of syringe and needle is not recommended as they may cause leakage.

All bags of Ceftazidime for Injection, USP as supplied are under reduced pressure. When Ceftazidime for Injection, USP is dissolved, carbon dioxide is released, and a positive pressure develops. Insert a gas-relief needle through the additive port of the SmartPak® bag to relieve the internal pressure. Remove the gas-relief needle before extracting any solution.

Note: To preserve product sterility, it is important that a gas-relief needle is *not* inserted through the additive port before the product has dissolved.

Solutions of Ceftazidime for Injection, USP, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with Ceftazidime for Injection, USP and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

COMPATIBILITY AND STABILITY

Ceftazidime for Injection, USP, when constituted as directed with Sterile Water for Injection, USP maintains satisfactory potency for 24 hours at room temperature, for 7 days under refrigeration, or for 3 months when stored at -20°C. Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator.

Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of Vancomycin and ceftazidime present. It is, therefore, recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines between the administration of these two agents.

Note: Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit.

As with other cephalosporins, Ceftazidime for Injection, USP powder, as well as solutions, tends to darken, depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

HOW SUPPLIED

Ceftazidime for Injection, USP in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Ceftazidime for Injection, USP is a dry, white to off-white powder supplied in a 100-gram plastic bag with foil outer wrap pharmacy bulk package NDC 66288-5100-1.

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol.* 1966; 45:493-496.

2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disc Susceptibility Tests.* (M2-A3). December 1984.

3. Certification procedure for antibiotic sensitivity discs (21 CFR 460.1). *Federal Register.* May 30, 1974; 39:19182-19184.

4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41.

SAMSON
MEDICAL TECHNOLOGIES, L.L.C.

Samson Medical Technologies, L.L.C.
Cherry Hill, NJ 08003, USA

Issued May 2003