SANDOZ

Appendix A

Wyeth's Old Formulation Physician Insert

ZOSYN®

(Piperacillin and Tazobactam for Injection)

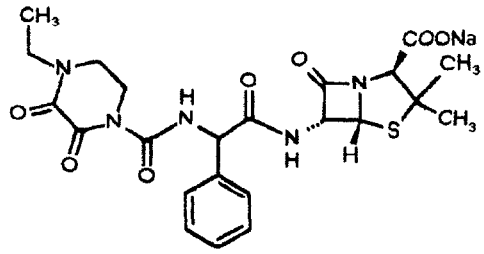
℞ only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zosyn (piperacillin and tazobactam) injection and other antibacterial drugs, Zosyn (piperacillin and tazobactam) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

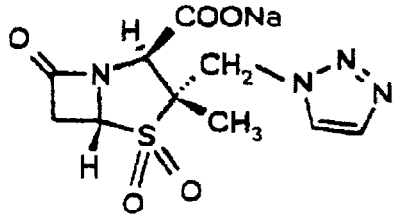
DESCRIPTION

Zosyn (piperacillin and tazobactam for injection) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration.

Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5. The chemical structure of piperacillin sodium is:



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3. The chemical structure of tazobactam sodium is:



Zosyn, piperacillin/tazobactam parenteral combination, is a white to off-white sterile, cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials. The product does not contain excipients or preservatives.

Each Zosyn 2.25 g single dose vial or ADD-Vantage® vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam.

Each Zosyn 3.375 g single dose vial or ADD-Vantage® vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam.

Each Zosyn 4.5 g single dose vial or ADD-Vantage® vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam.

Zosyn (piperacillin and tazobactam for injection) is a monosodium salt of piperacillin and a monosodium salt of tazobactam containing a total of 2.35 mEq (54 mg) of Na^+ per gram of piperacillin in the combination product.

CLINICAL PHARMACOLOGY

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of Zosyn. Piperacillin plasma concentrations, following a 30-minute infusion of Zosyn, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134, 242 and 298 μg/mL for the 2.25 g, 3.375 g and 4.5 g Zosyn (piperacillin/tazobactam) doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15, 24 and 34 μg/mL, respectively.

Following a 30-minute I.V. infusion of 3.375 g Zosyn every 6 hours, steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose. In like manner, steady-state plasma concentrations were not different from those attained after the first dose when 2.25 g or 4.5 g doses of Zosyn were administered via 30-minute infusions every 6 hours. Steady-state plasma concentrations after 30-minute infusions every 6 hours are provided in Table 1.

Following single or multiple Zosyn doses to healthy subjects, the plasma half-life of piperacillin and of tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion.

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50% to 100% of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 mL/min, the increase in half-life is twofold for piperacillin and fourfold for tazobactam compared to subjects with normal renal function. Dosage adjustments for Zosyn are recommended when creatinine clearance is below 40 mL/min in patients receiving the usual recommended daily dose of Zosyn (piperacillin and tazobactam for injection). (See **DOSAGE AND ADMINISTRATION** section for specific recommendations for the treatment of patients with renal insufficiency.)

Hemodialysis removes 30% to 40% of a piperacillin/tazobactam dose with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 16% of the tazobactam dose removed as the tazobactam metabolite. For dosage recommendations for patients undergoing hemodialysis, see **DOSAGE AND ADMINISTRATION** section.

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, this difference does not warrant dosage adjustment of Zosyn due to hepatic cirrhosis.

TABLE 1
STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS

PIPERACILLIN

		Plasma Concentrations** (μg/mL)						AUC** (μg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14)[b]	131 (14)
3.375 g	6	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1.0 (10)	242 (10)
4.5 g	8	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

TAZOBACTAM

		Plasma Concentrations** (μg/mL)						AUC** (μg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6)[c]	<0.5	16.0 (21)
3.375 g	6	24.2 (14)	10.7 (7)	4.0 (18)	1.4 (21)	0.7 (16)[b]	<0.5	25.0 (8)
4.5 g	8	33.8 (15)	17.3 (16)	6.8 (24)	2.8 (25)	1.3 (30)	<0.5	39.8 (15)

** Numbers in parentheses are coefficients of variation (CV%).
a: Piperacillin and tazobactam were given in combination.
b: N = 4
c: N = 3

Microbiology

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. In vitro, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium has little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is, however, a β-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated β-lactamases at tazobactam concentrations achieved with the recommended dosage regimen.

Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms:
Staphylococcus aureus (excluding methicillin and oxacillin-resistant isolates)

Aerobic and facultative Gram-negative microorganisms:
Acinetobacter baumanii
Escherichia coli
Haemophilus influenzae (excluding β-lactamase negative, ampicillin-resistant isolates)
Klebsiella pneumoniae
Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

Gram-negative anaerobes:
Bacteroides fragilis group (*B. fragilis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus*)

The following in vitro data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam. However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms:
Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)
Staphylococcus epidermidis (excluding methicillin and oxacillin resistant isolates)
Streptococcus agalactiae[†]
Streptococcus pneumoniae[†] (penicillin-susceptible isolates only)
Streptococcus pyogenes[†]
Viridans group streptococci[†]

Aerobic and facultative Gram-negative microorganisms:
Citrobacter koseri
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Serratia marcescens
Providencia stuartii
Providencia rettgeri
Salmonella enterica

Gram-positive anaerobes:
Clostridium perfringens

Gram-negative anaerobes:
Bacteroides distasonis
Prevotella melaninogenica

[†]These are not β-lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.

Susceptibility Testing Methods

As is recommended with all antimicrobials, the results of in vitro susceptibility tests, when available, should be provided to the physician as periodic reports, which describe the susceptibility profile of nosocomial and community-acquired pathogens These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of piperacillin and tazobactam powders.[1,2] MIC values should be determined using serial dilutions of piperacillin combined with a fixed concentration of 4 μg/mL tazobactam. The MIC values obtained should be interpreted according to criteria provided in Table 2.

Diffusion Technique:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 100 μg of piperacillin and 10 μg of tazobactam to test the susceptibility of microorganisms to piperacillin/tazobactam. The disk diffusion interpreted criteria are provided in Table 2.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method.[4]

TABLE 2
SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM

	Susceptibility Test Result Interpretive Criteria					
	Minimal Inhibitory Concentration (MIC in μg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae and *Acinetobacter baumanii*	≤ 16	32 - 64	≥ 128	≥ 21	18 - 20	≤ 17
Haemophilus influenzae[a]	≤ 1	-	≥ 2	-	-	-
Pseudomonas aeruginosa	≤ 64	-	≥ 128	≥ 18	-	≤ 17
Staphylococcus aureus	≤ 8	-	≥ 16	≥ 20	-	≤ 19
Bacteroides fragilis group	≤ 32	64	≥ 128	-	-	-

a: These interpretive criteria for *Haemophilus influenzae* are applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours.

A report of S ("Susceptible") indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of I ("Intermediate") indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of R ("Resistant") indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be considered.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures.[1,2,3,4] Standard piperacillin/tazobactam powder should provide the following ranges of values noted in Table 3. Quality control microorganisms are specific strains of microorganisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for microbiological quality control are not clinically significant.

TABLE 3
ACCEPTABLE QUALITY CONTROL RANGES FOR PIPERACILLIN/TAZOBACTAM TO BE USED IN VALIDATION OF SUSCEPTIBILITY TEST RESULTS

	Acceptable Quality Control Ranges	
QC Strain	Minimum Inhibitory Concentration Range (MIC in μg/mL)	Disk Diffusion Zone Diameter Ranges in mm
Escherichia coli ATCC 25922	1 - 4	24 - 30
Escherichia coli ATCC 35218	0.5 - 2	24 - 30
Pseudomonas aeruginosa ATCC 27853	1 - 8	25 - 33
Haemophilus influenzae[a] ATCC 49247	0.06 - 0.5	-
Staphylococcus aureus ATCC 29213	0.25 - 2	-
Staphylococcus aureus ATCC 25923	-	27 – 36
Bacteroides fragilis ATCC 25285	0.12 - 0.5	-
Bacteroides thetaiotaomicron ATCC 29741	4 - 16	-

a: This quality control range for *Haemophilus influenzae* is applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours.

INDICATIONS AND USAGE

Zosyn (piperacillin and tazobactam for injection) is indicated for the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, β-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, or *B. vulgatus*. The individual members of this group were studied in less than 10 cases.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by piperacillin-resistant, β-lactamase producing strains of *Staphylococcus aureus*.

Postpartum endometritis or pelvic inflammatory disease caused by piperacillin-resistant, β-lactamase producing strains of *Escherichia coli*.

Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant, β-lactamase producing strains of *Haemophilus influenzae*.

Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, β-lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter baumanii*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Nosocomial pneumonia caused by *P. aeruginosa* should be treated in combination with an aminoglycoside). (See **DOSAGE AND ADMINISTRATION**.)

Zosyn (piperacillin and tazobactam for injection) is indicated only for the specified conditions listed above. Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to Zosyn treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the activity of the piperacillin component against piperacillin-susceptible organisms. Therefore, the treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β-lactamase producing organisms susceptible to Zosyn should not require the addition of another antibiotic. (See **DOSAGE AND ADMINISTRATION**.)

Zosyn is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to Zosyn. Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zosyn (piperacillin and tazobactam) injection and other antibacterial drugs, Zosyn (piperacillin and tazobactam) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Zosyn is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH PENICILLINS INCLUDING ZOSYN. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ZOSYN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, ZOSYN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC/ ANAPHYLACTOID REACTIONS (INCLUDING SHOCK) REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including piperacillin/tazobactam, 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, 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.

PRECAUTIONS

General

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics, including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, Zosyn (piperacillin and tazobactam for injection) should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Zosyn is a monosodium salt of piperacillin and a monosodium salt of tazobactam and contains a total of 2.35 mEq (54 mg) of Na^+ per gram of piperacillin in the combination product. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be performed in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

As with other semisynthetic penicillins, piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

In patients with creatinine clearance ≤ 40 mL/min and dialysis patients (hemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal function impairment. (See **DOSAGE AND ADMINISTRATION**.)

Prescribing Zosyn (piperacillin and tazobactam) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

Information for Patients

Patients should be counseled that antibacterial drugs including Zosyn should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Zosyn is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Zosyn or other antibacterial drugs in the future.

Laboratory Tests

Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, ie, ≥ 21 days. (See **ADVERSE REACTIONS, Adverse Laboratory Events**.)

Drug Interactions

Aminoglycosides

The mixing of Zosyn with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. (See **DOSAGE AND ADMINISTRATION, Compatible Intravenous Diluent Solutions**.)

The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity. Coadministration of Zosyn with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly altered and should be monitored. Since aminoglycosides are not equally susceptible to inactivation by piperacillin, consideration should be given to the choice of the aminoglycoside when administered in combination with piperacillin to these patients.

Probenecid

Probenecid administered concomitantly with Zosyn prolongs the half-life of piperacillin by 21% and that of tazobactam by 71%.

Vancomycin

No pharmacokinetic interactions have been noted between Zosyn and vancomycin.

Heparin

Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Zosyn (piperacillin/tazobactam) could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

Methotrexate

Limited data suggests that co-administration of methotrexate and piperacillin may reduce the clearance of methotrexate due to competition for renal secretion. The impact of tazobactam on the elimination of methotrexate has not been evaluated. If concurrent therapy is necessary, serum concentrations of methotrexate as well as the signs and symptoms of methotrexate toxicity should be frequently monitored.

Drug/Laboratory Test Interactions

As with other penicillins, the administration of Zosyn® (piperacillin and tazobactam for injection) may result in a false-positive reaction for glucose in the urine using a copper-reduction method (CLINITEST®). It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as DIASTIX® or TES-TAPE®) be used.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving piperacillin/tazobactam injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with the Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported.

Therefore, positive test results in patients receiving piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam.

Piperacillin/Tazobactam

Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.86 μg/plate. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test at concentrations up to 5689/711 μg/mL. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 8000/1000 μg/mL. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay at concentrations up to 8/1 μg/mL. In vivo, piperacillin/ tazobactam did not induce chromosomal aberrations in rats dosed I.V. with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily dose on a body-surface-area basis (mg/m^2).

Piperacillin

Piperacillin was negative in microbial mutagenicity assays at concentrations up to 50 μg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 μg/disk. Piperacillin was negative in the UDS test at concentrations up to 10,000 μg/mL. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 μg/mL. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 3000 μg/mL. In vivo, piperacillin did not induce chromosomal aberrations in mice at I.V. doses up to 2000 mg/kg/day or rats at I.V. doses up to 1500 mg/kg/day. These doses are half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface area (mg/m^2). In another in vivo test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the maximum recommended human daily dose based on body-surface area (mg/m^2), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at I.V. doses up to 2000 mg/kg/day did not show increased mutation frequencies.

Tazobactam

Tazobactam was negative in microbial mutagenicity assays at concentrations up to 333 μg/plate. Tazobactam was negative in the UDS test at concentrations up to 2000 μg/mL. Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 5000 μg/mL. In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥3000 μg/mL. Tazobactam was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 900 μg/mL. In an in vitro cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 μg/mL. In vivo, tazobactam did not induce chromosomal aberrations in rats at I.V. doses up to 5000 mg/kg, which is 23 times the maximum recommended human daily dose based on body-surface area (mg/m^2).

Pregnancy

Teratogenic effects—Pregnancy Category B

Piperacillin/tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on body-surface area (mg/m^2).

Piperacillin and tazobactam cross the placenta in humans.

Piperacillin

Reproduction and teratology studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to piperacillin administered up to a dose which is half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface area (mg/m^2).

Tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the maximum recommended human daily dose based on body-surface area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on body-surface area (mg/m^2). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of those found in maternal plasma.

There are, however, no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when Zosyn (piperacillin and tazobactam for injection) is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients have not been established.

Geriatric Use
Patients over 65 years are **not** at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.
(See **DOSAGE AND ADMINISTRATION**.)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Zosyn contains 54 mg (2.35 mEq) of sodium per gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 648 and 864 mg/day (28.2 and 37.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

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.

ADVERSE REACTIONS
Adverse Events From Clinical Trials
During the initial clinical investigations, 2621 patients worldwide were treated with Zosyn (piperacillin and tazobactam for injection) in phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, Zosyn was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to therapy with Zosyn, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to Zosyn therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%), rhinitis (1.2%); and dyspnea (1.1%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials are listed below within each body system.

Autonomic nervous system—hypotension, ileus, syncope

Body as a whole—rigors, back pain, malaise

Cardiovascular—tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction

Central nervous system—tremor, convulsions, vertigo

Gastrointestinal—melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis

Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Hearing and Vestibular System—tinnitus

Hypersensitivity—anaphylaxis

Metabolic and Nutritional—symptomatic hypoglycemia, thirst

Musculoskeletal—myalgia, arthralgia

Platelets, Bleeding, Clotting—mesenteric embolism, purpura, epistaxis, pulmonary embolism (See **PRECAUTIONS, General**).

Psychiatric—confusion, hallucination, depression

Reproductive, Female—leukorrhea, vaginitis

Respiratory—pharyngitis, pulmonary edema, bronchospasm, coughing

Skin and Appendages—genital pruritus, diaphoresis

Special senses—taste perversion

Urinary—retention, dysuria, oliguria, hematuria, incontinence

Vision—photophobia

Vascular (extracardiac)—flushing

Nosocomial Pneumonia Trials

In a completed study of nosocomial lower respiratory tract infections, 222 patients were treated with Zosyn in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with imipenem/cilastatin (500 mg/500 mg q6h) in combination with an aminoglycoside. In this trial, treatment-emergent adverse events were reported by 402 patients, 204 (91.9%) in the piperacillin/tazobactam group and 198 (92.1%) in the imipenem/cilastatin group. Twenty-five (11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenem/cilastatin group ($p > 0.05$) discontinued treatment due to an adverse event.

In this study of Zosyn in combination with an aminoglycoside, adverse events that occurred in more than 1% patients and were considered by the investigator to be drug-related were: diarrhea (17.6%), fever (2.7%), vomiting (2.7%), urinary tract infection (2.7%), rash (2.3%), abdominal pain (1.8%), generalized edema (1.8%), moniliasis (1.8%), nausea (1.8%), oral moniliasis (1.8%), BUN increased (1.8%), creatinine increased (1.8%), peripheral edema (1.8%), abdomen enlarged (1.4%), headache (1.4%), constipation (1.4%), liver function tests abnormal (1.4%), thrombocythemia (1.4%), excoriations (1.4%), and sweating (1.4%).

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of Zosyn with an aminoglycoside were: acidosis, acute kidney failure, agitation, alkaline phosphatase increased, anemia, asthenia, atrial fibrillation, chest pain, CNS depression, colitis, confusion, convulsion, cough increased, thrombocytopenia, dehydration, depression, diplopia, drug level decreased, dry mouth, dyspepsia, dysphagia, dyspnea, dysuria, eosinophilia, fungal dermatitis, gastritis, glossitis, grand mal convulsion, hematuria, hyperglycemia, hypernatremia, hypertension, hypertonia, hyperventilation, hypochromic anemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, injection site edema, injection site pain, injection site reaction, kidney function abnormal, leukocytosis, leukopenia, local reaction to procedure, melena, pain, prothrombin decreased, pruritus, respiratory disorder, SGOT increased, SGPT increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

In a previous nosocomial pneumonia study conducted with a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside, the following adverse events, irrespective of drug relationship, were observed: diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Adverse events irrespective of drug relationship observed in 1% or less of patients in the above study with Zosyn and an aminoglycoside included: aggressive reaction (combative), angina, asthenia, atelectasis, balanoposthitis, cerebrovascular accident, chest pain, conjunctivitis, deafness, dyspnea, earache, ecchymosis, fecal incontinence, gastric ulcer, gout, hemoptysis, hypoxia, pancreatitis, perineal irritation/pain, urinary tract infection with trichomonas, vitamin B_{12} deficiency anemia, xerosis, and yeast in urine.

Post-Marketing Experience

Additional adverse events reported from worldwide marketing experience with Zosyn, occurring under circumstances where causal relationship to Zosyn is uncertain:

Gastrointestinal—hepatitis, cholestatic jaundice

Hematologic—hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia

Immune—hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock)

Infections—candidal superinfections

Renal—interstitial nephritis, renal failure

Skin and Appendages—erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Adverse Laboratory Events (Seen During Clinical Trials)

Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of Zosyn (piperacillin and tazobactam for injection) was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include:

Hematologic—decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia associated with Zosyn administration appears to be reversible and most frequently associated with prolonged administration, ie, ≥21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (eg, fever, rigors, chills).

Coagulation—positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time

Hepatic—transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin

Renal—increases in serum creatinine, blood urea nitrogen

Urinalysis—proteinuria, hematuria, pyuria

Additional laboratory events include abnormalities in electrolytes (ie, increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time prolonged.

The following adverse reaction has also been reported for PIPRACIL® (piperacillin for injection):

Skeletal—prolonged muscle relaxation (See **PRECAUTIONS, Drug Interactions**.)

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

OVERDOSAGE

There have been postmarketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhea, have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment should be supportive and symptomatic according the patient's clinical presentation. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis. Following a single 3.375 g dose of piperacillin/tazobactam, the percentage of the piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively. (See **CLINICAL PHARMACOLOGY**.)

DOSAGE AND ADMINISTRATION

Zosyn should be administered by intravenous infusion over 30 minutes.

The usual total daily dose of Zosyn for adults is 3.375 g every six hours totaling 13.5 g (12.0 g piperacillin/1.5 g tazobactam).

Initial presumptive treatment of patients with nosocomial pneumonia should start with Zosyn at a dosage of 4.5 g every six hours plus an aminoglycoside, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Renal Insufficiency

In patients with renal insufficiency (Creatinine Clearance ≤ 40 mL/min), the intravenous dose of Zosyn (piperacillin and tazobactam for injection) should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Zosyn for patients with renal insufficiency are as follows:

Recommended Dosing of Zosyn in Patients with Normal Renal Function and Renal Insufficiency
(As total grams piperacillin/tazobactam)

Renal Function (Creatinine Clearance, mL/min)	All Indications (except nosocomial pneumonia)	Nosocomial Pneumonia
>40 mL/min	3.375 q 6 h	4.5 q 6 h
20-40 mL/min*	2.25 q 6 h	3.375 q 6 h
<20 mL/min*	2.25 q 8 h	2.25 q 6 h
Hemodialysis**	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h

* Creatinine clearance for patients not receiving hemodialysis
** 0.75 g should be administered following each hemodialysis session on hemodialysis days

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g Zosyn should be administered following each dialysis period on hemodialysis days. No additional dosage of Zosyn is necessary for CAPD patients.

Duration of Therapy

The usual duration of Zosyn treatment is from seven to ten days. However, the recommended duration of Zosyn treatment of nosocomial pneumonia is 7 to 14 days. In all conditions, the duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Directions for Reconstitution and Dilution for Use
Intravenous Administration

For conventional vials, reconstitute Zosyn per gram of piperacillin with 5 mL of a compatible reconstitution diluent from the list provided below.

2.25 g, 3.375 g, and 4.5 g Zosyn should be reconstituted with 10 mL, 15 mL, and 20 mL, respectively. Swirl until dissolved.

Pharmacy vials should be used immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C [68°F to 77°F]), or after 48 hours if stored at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Compatible Reconstitution Diluents

0.9% Sodium Chloride for Injection
Sterile Water for Injection‡
Dextrose 5%
Bacteriostatic Saline/Parabens
Bacteriostatic Water/Parabens
Bacteriostatic Saline/Benzyl Alcohol
Bacteriostatic Water/Benzyl Alcohol

Reconstituted Zosyn solution should be further diluted (recommended volume per dose of 50 mL to 150 mL) in a compatible intravenous diluent solution listed below. Administer by infusion over a period of at least 30 minutes. During the infusion it is desirable to discontinue the primary infusion solution.

Compatible Intravenous Diluent Solutions

0.9% Sodium Chloride for Injection
Sterile Water for Injection‡
Dextrose 5%
Dextran 6% in Saline

‡ Maximum recommended volume per dose of Sterile Water for Injection is 50 mL.

ADD-Vantage® System Admixtures

Dextrose 5% in Water (50 or 100 mL)
0.9% Sodium Chloride (50 or 100 mL)

For ADD-Vantage® vials reconstitution directions, see *INSTRUCTIONS FOR USE* sheet provided in the box.

Zosyn should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Zosyn is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

LACTATED RINGER'S SOLUTION IS NOT COMPATIBLE WITH ZOSYN.
Zosyn should not be added to blood products or albumin hydrolysates.

When concomitant therapy with aminoglycosides is indicated, Zosyn and the aminoglycoside should be reconstituted and administered separately, due to the in vitro inactivation of the aminoglycoside by the penicillin. (See PRECAUTIONS, Drug Interactions.)

Zosyn can be used in ambulatory intravenous infusion pumps.

Stability of Zosyn Following Reconstitution

Zosyn is stable in glass and plastic containers (plastic syringes, I.V. bags and tubing) when used with compatible diluents.

Pharmacy vials should be used immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C [68°F to 77°F]), or after 48 hours if stored at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Vials should not be frozen after reconstitution.

Stability studies in the I.V. bags have demonstrated chemical stability (potency, pH of reconstituted solution and clarity of solution) for up to 24 hours at room temperature and up to one week at refrigerated temperature. Zosyn contains no preservatives. Appropriate consideration of aseptic technique should be used.

Stability of Zosyn in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature. Each dose was reconstituted and diluted to a volume of 37.5 mL or 25 mL. One-day supplies of dosing solution were aseptically transferred into the medication reservoir (I.V. bags or cartridge). The reservoir was fitted to a preprogrammed ambulatory intravenous infusion pump per the manufacturer's instructions. Stability of Zosyn is not affected when administered using an ambulatory intravenous infusion pump.

Stability studies with the admixed ADD-Vantage® system have demonstrated chemical stability (potency, pH and clarity) through 24 hours at room temperature. (Note: The admixed ADD-Vantage® should not be refrigerated or frozen after reconstitution.) Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Zosyn® (piperacillin and tazobactam for injection) is supplied in the following sizes:

Each Zosyn 2.25 g vial provides piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. Each vial contains 4.69 mEq (108 mg) of sodium.

Supplied 10 per box—NDC 0206-8452-16

Each Zosyn 3.375 g vial provides piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. Each vial contains 7.04 mEq (162 mg) of sodium.

Supplied 10 per box—NDC 0206-8454-55

Each Zosyn 4.5 g vial provides piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each vial contains 9.39 mEq (216 mg) of sodium.

Supplied 10 per box—NDC 0206-8455-25

Each Zosyn 2.25 g ADD-Vantage® vial provides piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. Each ADD-Vantage® vial contains 4.69 mEq (108 mg) of sodium.

Supplied 10 per box—NDC 0206-8452-17.

Each Zosyn 3.375 g ADD-Vantage® vial provides piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. Each ADD-Vantage® vial contains 7.04 mEq (162 mg) of sodium.

Supplied 10 per box—NDC 0206-8454-17.

Each Zosyn 4.5 g ADD-Vantage® vial provides piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each ADD-Vantage® vial contains 9.39 mEq (216 mg) of sodium.

Supplied 10 per box—NDC 0206-8455-17.

Zosyn conventional and ADD-Vantage® vials should be stored at controlled room temperature (20°C to 25°C [68°F to 77°F]) prior to reconstitution.

Also Available

Zosyn® (piperacillin and tazobactam injection) in Galaxy® Container (PL 2040 Plastic) is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in single dose plastic containers as follows:

2.25 g (piperacillin sodium equivalent to 2 g piperacillin/tazobactam sodium equivalent to 0.25 g tazobactam) in 50 mL. Each container has 5.7 mEq (131 mg) of sodium. Supplied 24/box—NDC 0206-8820-02

3.375 g (piperacillin sodium equivalent to 3 g piperacillin/tazobactam sodium equivalent to 0.375 g tazobactam) in 50 mL. Each container has 8.6 mEq (197 mg) of sodium. Supplied 24/box—NDC 0206-8821-02

4.5 g (piperacillin sodium equivalent to 4 g piperacillin/tazobactam sodium equivalent to 0.5 g tazobactam) in 100 mL. Each container has 11.4 mEq (263 mg) of sodium. Supplied 12/box—NDC 0206-8822-02

Also Available

Zosyn (piperacillin and tazobactam for injection) is supplied as a powder in the pharmacy bulk vial as follows:

40.5 g pharmacy bulk vial containing piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 4.5 grams of tazobactam. Each pharmacy bulk vial contains 84.5 mEq (1,944 mg) of sodium. NDC 0206-8620-11

REFERENCES

1. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Testing; 13th Informational Supplement. NCCLS document M100-S13. NCCLS, Wayne, PA, 2003.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically; Approved Standard—5th Edition. NCCLS document M7-A5. NCCLS, Wayne, PA, 2000.

3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Test; Approved Standard—8th Edition. NCCLS document M2-A8. NCCLS, Wayne, PA, 2003.

4. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard—5th ed. NCCLS document M11-A5. NCCLS, Wayne, PA, 2001.

CLINITEST® and DIASTIX® are registered trademarks of Ames Division, Miles Laboratories, Inc.

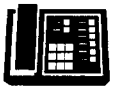
TES-TAPE® is a registered trademark of Eli Lilly and Company.

Galaxy® is a registered trademark of Baxter International, Inc.

ADD-Vantage® is a registered trademark of Abbott Laboratories.

U.S. Patent No. 4,562,073

For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.



Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

W10414C006
ET01
Rev 07/05