PRODUCT MONOGRAPH

[Pr]Piperacillin for Injection
(Piperacillin Sodium)

2 g, 3 g and 4 g piperacillin per vial

Hospira Standard

Antibiotic

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Date of Revision:
March 8, 2018

Control Number: 203911

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ACTIONS AND CLINICAL PHARMACOLOGY

Piperacillin is a semi-synthetic beta-lactam antibiotic which is bactericidal and exerts its antibacterial action by inhibiting both septum and cell wall synthesis in the bacterial cell.

Piperacillin was shown to have a particularly high affinity for PBP-3 and also a high affinity for PBP-1A, -lB and -2 of *Escherichia coli* and *pseudomonas*. These results indicate that the enzymes involved in septum (PBP-3) and cell-wall (PBP-lA, -1B) synthesis and in the maintenance of the shape (PBP-2) of the bacterium are the primary sites of action of piperacillin.

Piperacillin is eliminated primarily (60-80%) by glomerular filtration and tubular secretion as unchanged drug in the urine. The mean elimination half-life is 54 minutes after the administration of 2 grams and 63 minutes following 6 grams. The elimination half-life is increased two-fold in mild to moderate renal impairment and five- to six-fold in severe renal impairment.

INDICATIONS AND CLINICAL USES

Piperacillin for Injection is recommended for the treatment of systemic and local infections due to susceptible strains of gram-negative and gram-positive aerobic and anaerobic bacteria listed below. Because of its broad spectrum of activity, Piperacillin for Injection is also suitable for the therapy of mixed infections, and the presumptive therapy of serious infections, when piperacillin-sensitive pathogens are suspected as the cause of disease.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin for Injection and other antibacterial drugs, Piperacillin for Injection should be used only to treat 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.

a) INTRA-ABDOMINAL INFECTIONS, including hepato-biliary and surgical infections caused by *Escherichia coli*, *Pseudomonas aeruginosa*, enterococci, *Clostridium* spp., anaerobic cocci, and Bacteroides spp., including *B. fragilis*.

b) URINARY TRACT INFECTIONS, (complicated and uncomplicated) caused by *Escherichia coli*, *Klebsiella* spp., *Pseudomas aeruginosa*, *Proteus mirabilis* and enterococci.

c) GYNECOLOGICAL INFECTIONS, including endometritis and pelvic inflammatory disease, caused by *Bacteroides* spp., including *B. fragilis*, anaerobic cocci, *Neisseria gonarrhoeae*, and enterococci (*Streptococcus faecalis*).

d) SEPTICEMIA, including bacteremia caused by *Escherichia coli*, *Klebsiella* spp., *Serratia* spp., *Proteus mirabilis*, *S. pneumoniae*, enterococci, *Pseudomonas aeruginosa*, *Bacteroides* spp., and anaerobic cocci.

e) LOWER RESPIRATORY TRACT INFECTIONS, caused by *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, *Serratia* spp., *Haemophilus influenzae*, *Bacteroides* species and anaerobic cocci. Although improvement has been noted in patients with cystic fibrosis, lasting bacterial eradication may not be achieved.

f) SKIN AND SKIN STRUCTURE INFECTIONS, caused by *Escherichia coli*, *Klebsiella* spp., *Serratia* spp., *Acinetobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, indole-positive *Proteus* spp., *Proteus mirabilis*, *Bacteroides* spp., including *B. fragilis*, anaerobic cocci and enterococci.

g) BONE AND JOINT INFECTIONS, caused by *Pseudomonas aeruginosa*, enterococci, *Bacteroides* spp., and anaerobic cocci.

h) Uncomplicated urethritis caused by *Neisseria gonorrhoeae*.

Appropriate cultures should be made before initiating treatment. Presumptive therapy may be started while awaiting results of susceptibility tests. Treatment should be adjusted, if necessary, when results of these tests become available.

MIXED INFECTIONS

Piperacillin for Injection has also been shown to be clinically effective for the treatment of infections at various sites caused by streptococcus species, including Group A beta-hemolytic *Streptococcus* and *Streptococcus pneumoniae*. While infections caused solely by these organisms are ordinarily treated with narrower spectrum penicillins, mixed infections involving the above, and other organisms susceptible to piperacillin, may be effectively treated by the latter.

Piperacillin for Injection may be administered as single drug therapy in some situations where normally two antibiotics might be employed.

GENERAL
The efficacy of Piperacillin for Injection has been demonstrated in infections produced by organisms resistant to other penicillins, some aminoglycosides and cephalosporins.

Combined Therapy with Other Antibiotics
In vitro synergism has been shown between piperacillin and some aminoglycosides in some bacterial strains. Piperacillin for Injection has been used clinically with aminoglycosides, especially in patients with impaired host defenses. Both drugs were used in full therapeutic doses.

Piperacillin for Injection can be used safely in combination with penicillinase-resistant penicillins, e.g. oxacillin, in mixed infections when beta-lactamase-positive *Staphylococcus aureus* is isolated along with piperacillin-susceptible organisms.

Piperacillin for Injection may be administered concomitantly with a cephalosporin, provided that an additive or synergistic antibacterial action of the two antibiotics is ascertained through *in vitro* tests. Based on *in vitro* data, cefoxitin should not be given with piperacillin when infections caused by organisms producing inducible β-lactamases are suspected or confirmed.

CONTRAINDICATIONS

A history of allergic reactions to any of the penicillins and/or cephalosporins.

Piperacillin for Injection when reconstituted with Lidocaine for intramuscular use is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

Cross-sensitivity of patients to penicillins and cephalosporins has been reported. Before initiating therapy with Piperacillin for Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens.

If an allergic reaction occurs, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines and corticosteroids) should be readily available.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS NECESSARY.

Antibiotic-associated pseudomembranous colitis has been reported with nearly all antibacterial agents, including piperacillin, and may range in severity from mild to life-threatening. It is important to consider this diagnosis if significant diarrhea or colitis occurs during therapy. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *Clostridium difficile* (e.g., oral vancomycin) should be considered.

PRECAUTIONS

While Piperacillin for Injection possesses the characteristic low toxicity of the penicillin group of antibiotics, it is advisable to check periodically for organ dysfunction (including renal, hepatic and hematopoietic) during prolonged therapy.

Bleeding manifestations have occurred in some patients receiving beta-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 or significant leukopenia occur, Piperacillin for Injection should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms and the development of superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses of Piperacillin for Injection are given intravenously.

Since Piperacillin for Injection is excreted not only renally but also by the biliary route, it can be used at reduced dosage (see **DOSAGE and ADMINISTRATION**) in patients with severely restricted kidney function and in those who have had nephrotoxic reactions to other drugs.

Piperacillin for Injection is a monosodium compound containing 1.85 milliequivalents (42.5 mg) of Na^+ per gram based on molecular weight (see **PHARMACEUTICAL INFORMATION**). This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves, receiving cytotoxic therapy or diuretics. Electrolyte and cardiac status should also be monitored during prolonged treatment in patients with impaired cardiac function.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from

patients with any suspected primary lesion, and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

The use of some penicillins (ampicillin, amoxicillin) has been associated with morbilliform rashes in some cases of infectious mononucleosis. Piperacillin for Injection should therefore be used with caution in the treatment of infections caused by susceptible organisms in patients with infectious mononucleosis.

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

Because of chemical instability, Piperacillin for Injection should not be used for intravenous administration with solutions containing only Sodium Bicarbonate (see **PHARMACEUTICAL INFORMATION:** Incompatibility). Piperacillin for Injection should not be added to blood products.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing Piperacillin for Injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Drug Interactions
The mixing of Piperacillin for Injection with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Concurrent administration of probenecid results in higher and more prolonged serum levels of piperacillin.

Whenever Piperacillin for Injection is administered concurrently with another antibiotic the drugs should not be mixed in the same solution but must be administered separately.

Piperacillin, when used clinically in the early postoperative period, has been implicated in the prolongation of the neuromuscular blockage of vecuronium. In a controlled clinical study, the ureidopenicillins including piperacillin have been reported to prolong the action of vecuronium. Caution is indicated when piperacillin is used perioperatively with vecuronium and similar neuromuscular blocking agents.

Usage During Pregnancy or Lactation
Although reproduction studies in mice and rats performed at doses up to 4 times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of Piperacillin for Injection use in pregnant women has not been determined. Because animal reproduction studies

are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

Caution should be exercised when Piperacillin for Injection is administered to nursing mothers. It is excreted in low concentrations in milk.

Pediatric Use
Dosage for children under the age of 12 have not been established.

ADVERSE REACTIONS

Piperacillin for Injection is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur:

Local Reactions
In adult clinical trials, thrombophlebitis was noted in 2.5% of patients. It is more likely to occur when an insufficiently diluted solution is injected into the vein.

Pain, erythema, and/or induration at the injection site occurred in 1% of patients. Less frequent reactions, including ecchymosis, deep vein thrombosis and hematomas, have also occurred.

Hypersensitivity Reactions
Rash and/or pruritus was noted in 2.3% of patients. Drug fever was 2% (Note: The incidence of rash and fever is higher in patients with cystic fibrosis). Other less frequent findings included vesicular eruptions, positive Coombs tests. Anaphylactoid reactions have been reported rarely (see **WARNINGS**). Other dermatologic manifestations such as erythema multiforme, Stevens-Johnson Syndrome and Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS) have been reported rarely. DRESS has notably been reported when piperacillin was used in combination with tazobactam.

Gastrointestinal
Diarrhea and loose stools were noted in 3% of patients. Other less frequent reactions included vomiting, nausea and bloody diarrhea. Pseudomembranous colitis has been reported rarely.

Hepatic
Increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia. Rarely, cholestatic hepatitis.

Renal
Elevations of creatinine or BUN and rarely interstitial nephritis.

Central Nervous System
Headache, dizziness, fatigue. Convulsions with high doses.

Hemic and Lymphatic
Reversible leukopenia, neutropenia, thrombocytopenia and/or eosinophilia, bleeding and decreases in prothrombin time have been reported. As with other beta-lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

Serum Electrolytes
Individuals with liver disease or individuals receiving cytotoxic therapy or diuretics, were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of Piperacillin for Injection.

Musculo-Skeletal
Rarely, prolonged muscle relaxation.

Other
Superinfection, including candidiasis and hemorrhagic manifestations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Other than general supportive treatment, no specific antidote is known. Excessive serum levels of piperacillin may be reduced by hemodialysis. As with other penicillins, neuromuscular excitability or convulsions have occurred following large intravenous doses. General supportive measures, including administration of phenytoin and barbiturates or other anticonvulsant drugs may be considered. Daily doses of piperacillin of at least 24 g have been administered to humans without observation of adverse effects. For treatment of hypersensitivity reactions, see **WARNINGS**.

DOSAGE AND ADMINISTRATION

Dosage
Piperacillin for Injection may be administered intramuscularly or intravenously (either in a 3 to 5 minute injection or by infusion). Dosage and route of administration should be determined by the severity of the infection and condition of the patient.

The usual dosage of Piperacillin for Injection for serious infections is 3 to 4 g given every 4 to 6 hours as a 20 to 30 minute infusion. For serious infections the intravenous route should be used.

The maximum daily dose usually administered to adults is 24 g/day, although higher doses have been used.

DOSAGE RECOMMENDATIONS

TYPE OF INFECTION ADMINISTRATION	USUAL TOTAL DAILY	FREQUENCY OF DOSAGE
Serious infections such as septicemia, nosocomial pneumonia, intra-abdominal infections, aerobic and anaerobic gynecologic infections, and skin and soft tissue infections	12-18 g IV (200-300 mg/kg)	Every 4 to 6 hours
Complicated urinary tract infections	8-16 g IV (125-200 mg/kg)	Every 6 to 8 hours
Uncomplicated urinary tract infections and most community-acquired pneumonia	6-8 g IM or IV (100-125mg/kg)	Every 6 to 12 hours
Uncomplicated gonococcal urethritis	2 g IM*	Single dose

*One gram of probenecid given orally 2 hour prior to injection.

DOSAGE IN RENAL IMPAIRMENT (ADULTS)

Degree of Renal Impairment	**Creatinine Clearance (mL/min)**	**Serum Level (mg%)**	**Urinary Tract Infection (Uncomplicated)**	**Urinary Tract Infection (complicated)**	**Serious Systemic Infection**
Mild	>40	1.5-3.0	N/A**	N/A**	N/A**
Moderate	20-40	3.1-5.0	N/A**	9 g/day (3 g q 8h)	12 g/day (4 g q 8h)
Severe	<20	>5	6 g/day (3 g q 12h)	6 g/day (3 g q 12h)	8 g/day (4 g q 12h)
Patients on Hemodialysis***					6 g/day (2 g q 8h)

N/A** No adjustment necessary

***Hemodialysis removes 30-50% of the drug in 4 hours; an additional dose of 1 g of Piperacillin for Injection should be administered following each dialysis period. For patients with renal failure, hepatic insufficiency or biliary tract obstruction measurement of serum levels of Piperacillin for Injection will provide additional guidance for adjusting dosage.

Infants and Children

Dosages in infants and children under 12 years of age have not been established.

Duration of Therapy

The average duration of Piperacillin for Injection treatment is from 7 to 10 days, except in the treatment of gynecologic infections, in which it is from 3 to 10 days; the duration should be

guided by the patient's clinical and bacteriological progress. Some infections such as osteomyelitis may require significantly longer periods of therapy. For most acute infections, treatment should be continued for at least 48 to 72 hours after the patient becomes asymptomatic. Antibiotic therapy for Group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to reduce the risk of rheumatic fever or glomerulonephritis.

Administration

Intramuscular Injection

Intramuscular injections should be limited to 2 g per injection site. This route of administration has been used primarily in the treatment of patients with uncomplicated gonorrhea and urinary tract infections. Injection should be given into the upper outer quadrant of the buttock (i.e. gluteus maximus).

When indicated by clinical and bacteriological findings, intramuscular administration of 6 to 8 g daily of Piperacillin for Injection, in divided doses, may be utilized for initiation of therapy. In addition, intramuscular administration of the drug may be considered for maintenance therapy after clinical and bacteriological improvement has been obtained with intravenous Piperacillin for Injection treatment.

The deltoid area should be used only if well-developed, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower or mid-third of the upper arm.

Intravenous Injection (Bolus)

Reconstituted solution should be injected slowly over a 3 to 5 minute period to help avoid vein irritation.

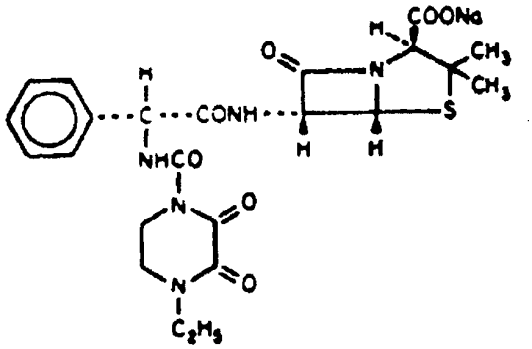
Intravenous Infusion

Infusion should be carried out over a period of about 20-40 minutes or intermittent infusion over a 30-minute to 2-hour period. During infusion, it is desirable to discontinue the primary intravenous solution.

PHARMACEUTICAL INFORMATION

Drug Substance
Proper Name: Piperacillin Sodium
Chemical Name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2α,5α,6β(S*)]].

Structural Formula:



Molecular Formula: $C_{23}H_{26}N_5NaO_7S$

Molecular Weight: 539.54

pH: 5.0-7.0, 100 mg/mL in carbon dioxide-free water.
Melting Point: 183-185 °C (decomposition).
Solubility: Freely soluble in water and in methanol, practically insoluble in ethyl acetate.

Description: Piperacillin sodium is a white to off-white hygroscopic powder.

Composition: Vials contain lyophilized (Freeze-dried) piperacillin sodium. The sodium content (Na^+), based on the molecular weight, is 1.85 mEq/g (42.5 mg/g).

Stability and Storage Recommendations
Stability studies have demonstrated chemical stability (pH, potency and clarity) through 24 hours at room temperature and up to 72 hours refrigerated, once reconstituted and stored in glass vials.

Stability of Solutions
Stability studies have demonstrated chemical stability (pH, potency and clarity) through 24 hours at room temperature and up to 72 hours refrigerated, upon further dilution in recommended intravenous solutions and intravenous admixtures when stored in plastic containers.

Incompatibility

Piperacillin for Injection should not be added to blood products.

Storage
Piperacillin for Injection vials should be stored at between 15 and 30°C, protected from light.

Parenteral Products
Reconstitution

For Intramuscular Use
Solutions for Reconstitution
Sterile water for injection or 0.5 -to 1.0% Lidocaine HCl (without Epinephrine) in sterile water for injection. (Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type).

Reconstitution Table

Vial Size	Volume to be added	Approximate Available Volume	Approximate Available Concentration
2 g	4.0 mL	5.0 mL	0.4 g/mL
3 g	6.0 mL	7.5 mL	0.4 g/mL
4 g	8.0 mL	10.0 mL	0.4 g/mL

Shake well until dissolved.

Note: Intramuscular injections should be limited to 2 g per injection site. Injection should be given into the upper outer quadrant of the buttock (i.e. gluteus maximus).

For Intravenous Injection or Infusion
For intravenous injection or infusion, reconstitute Piperacillin for Injection with sterile water for injection.

Reconstitution Table

Vial Size	Volume of Diluent to be added	Approximate Available Volume	Approximate Average Concentration
2 g	10 mL	11 mL	0.18 g/mL
3 g	15 mL	17 mL	0.18 g/mL
4 g	20 mL	22 mL	0.18 g/mL

Shake well until dissolved.

The prepared solution may be further diluted to the desired volume (at least 15 mL/g for infusion) with any Intravenous Solutions or Intravenous Admixtures listed below.

Intravenous Solutions:

Dextrose 5% in Water (D_5W)
0.9% Sodium Chloride (NORMAL SALINE) [NS]
Dextrose 5% and 0.9% Sodium Chloride (D_5NS)
Lactated Ringer's Injection
Dextran 6% in 0.9% Sodium Chloride

Intravenous Admixtures

Normal Saline [+ KCl 40 mEq/500 mL]
5% Dextrose in Water (D_5W) [+ KCl 40 mEq/500 mL]
5% Dextrose/Normal Saline (D_5NS) [+KCl 40 mEq/500 mL]
Ringer's Injection [+KCl 40 mEq/500 mL]
Lactated Ringer's Injection, [+KCl 40 mEq/500 mL]

Diluted Solutions

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Piperacillin for Injection is available in vials containing amounts of piperacillin sodium equivalent to 2, 3 and 4 grams of piperacillin. Available in boxes of 10 vials for the 2 g and 3 g formats and in boxes of 4 for the 4 g format. Single-use vials.

MICROBIOLOGY

Piperacillin is a bactericidal, semi-synthetic penicillin with a broad spectrum of activity, encompassing both gram-negative and gram-positive anaerobic and aerobic organisms. TABLE 1, lists the minimal inhibitory concentrations (MICs) of piperacillin for 47,119 clinical isolates tested *in vitro*.

TABLE I
In Vitro Activity of Piperacillin against 47,119 Clinical Isolates

Bacteria	No. of Isolates Tested	% of Isolates Inhibited by (mcg/mL)					
		1**	8	16	32	64	128
GRAM-NEGATIVE							
Acinetobacter spp.	481		34	73	80	85	95
Citrobacter spp.	619		72	77	80	83	94
Enterobacter spp.	4,023		73	79	84	88	91
Escherichia coli	8,363		70	76	76	85	89
Haemophilus Influenzae*	756	92	96	100			
Klebsiella pneumoniae	3,538		61	70	74	86	91
Klebsiella spp.	2,079		36	47	57	65	71
Moraxella spp.	22		100				
Neisseria gonorrhoeae	265	92	99	99			
Neisseria gonorrhoeae	44	100	100				
(β-lac)	107	97	100				
Neisseria meningitidis	2,747		79	83	88	92	95
Proteus(indole) spp.	3,903		89	91	93	95	97
Proteus mirabilis	118		36	39	39	43	69
Providencia spp.	8,604		65	80	91	95	98
Pseudomonas aeruginosa	1,961		61	73	81	86	94
Pseudomonas spp.	360		70	74	76	78	80
Salmonella spp.	1,394		58	67	72	81	85
Serratia marcescens	148		71	76	82	89	92
Shigella spp.	10		70	80	90	100	
Yersinia spp.							
ANAEROBES							
Bacteroides fragilis	524		51	72	90	94	97
Bacteroides spp.	576		49	63	83	91	94
Clostridium spp.	90		97	99	98	100	
Eubacterium spp.	76		67	71	87	89	92
Fusobacterium spp.	54		68	70	83	96	98
Peptococcus spp.	197		88	88	89	94	95
Peptostreptococcus spp.	185		88	91	94	95	95
Veillonella	32		84	84	91	100	
GRAM-POSITIVE							
Entercocci	1,100		90	92	93	94	95
Staphylococcus aureus*	3,162	18	69	80			
Staphylococcus epidermidis*	635	28	83	88			
Streptococcus agalactiae	45		100				
Streptococcus β-hemolytic	32		100				
Streptococcus pneumoniae	314		100				
Streptococcus pyogenes	475		100				
Streptococcus viridans	49		100				
Streptococcus spp.	31		100				

* Includes strains of both beta-lactamase positive and negative bacteria.
** Values at 1 mcg/mL given only for those species for which this is the recommended breakpoint.

Several investigators have shown that, for about 80% of clinical isolates of both gram-negative and gram-positive bacteria that were tested, the minimum bactericidal concentration (MBC) of piperacillin was equal to or at most twice the MIC. For the majority of the remaining 20% of isolates, the MBC/MlC ratio is 4/1. Overall, the MBC/MIC ratio of piperacillin is similar to that

of the aminoglycosides. Piperacillin kills isolates of *Pseudomonas* at about the same rate as cefoperazone and is 2-to 4- fold more active than moxalactam.

Table 2 lists the susceptibility of 9,725 clinical isolates of gram-negative aerobic and anaerobic isolates to piperacillin. The data were obtained during 1988 from 11 geographically distinct hospital laboratories throughout the United States. Susceptibility studies of gram-positive pathogens to piperacillin were not included in this study.

TABLE 2
In Vitro Activity of Piperacillin against 9,725 Clinical Isolates

ORGANISMS	Total #	Percent of Isolates		
		S* **≤16 mcg/mL**	**I*** **32-64 mcg/mL**	**R*** **≥128 mcg/mL**
Acinetobacter spp.	281	80	18	2
Bacteroides fragilis	293	58	25	17
Citrobacter diversus	122	89	7	4
Citrobacter freundil	227	73	13	14
Enterobacter aerogenes	330	64	30	5
Enterobacter cloacae	599	71	21	9
Escherichia coli	3500	79	9	12
Klebsiella pneumoniae	984	81	12	7
Klebsiella oxytoca	205	88	6	6
Morganella morganii	146	81	14	5
Proteus mirabilis	694	96	2	2
proteus vulgaris	57	98	2	0
Providencia rettgen	14	100	0	0
Providencia stuartii	36	78	17	6
Pseudomonas aeruginosa	1779	89	8	4
Pseudomonas spp.	195	37	39	24
Serratia marcescens	263	94	3	3
TOTAL (average)	9725	(80)	(13)	(7)

*S = Susceptible, I = Intermediate, R = Resistant

In vitro piperacillin is active against most strains of clinical isolates of the following microorganisms:

Aerobic and facultatively anerobic organisms

Gram-negative bacteria

Escherichia coli
Proteus mirabilis
*Proteus vulgaris**
*Morganella morganii** (formerly Proteus morganii)
*Providencia rettgen** (formerly Proteus rettgeri)
Serratia spp. including *S. marcescens** and *S. liquefaciens**
*Klebsiella pneumoniae**
Klebsiella spp.

Enterobacter spp. including *E. aerogenes** and *E. cloacae**
Citrobacter spp. including *C. freundii** and *C. diversus**
Salmonella spp.*
Shigella spp.*
Pseudomonas aeruginosa
Pseudomonas spp. including *P. cepacia*, P. maltophilia*, P. fluorescens**
Acinetobacter spp. (formerly *Mima-Herellea)*
Haemophilus influenzae (non-β-lactamase-producing strains)
Neisseria gonorrhoeae
*Neisseria meningitidis**
Moraxella spp.*
Yersinia spp.* (formerly *Pasteurella)*

Gram-positive bacteria

Group D Streptococci including Enterococci (Streptococcus faecalis, S. faecium*)
β-hemolytic streptococci including
Group A Streptococcus (S. pyogenes*)
Group B Streptococcus (S. agalactiae*)
Streptococcus pneumoniae
Streptococcus viridans*
Staphylococcus aureus (non-penicillinase-producing)*
Staphylococcus epidermidis (non-penicillinase-producing)*
Anaerobic bacteria
Bacteroides spp. including B. fragilis group (B. fragilis, B. vulgatus*)
Non-B fragilis group (B. melaninogenicus*)
B asaccharolyticus*
Clostridium spp. including C. perfringens* and C. difficile*
Eubacterium spp.
Fusobacterium spp.* including F. necleatum* and F. necrophorum*
Peptococcus spp.*
Peptostreptococcus spp.
Veillonella spp.*

*Piperacillin has been shown to be active *in vitro* against these organisms; however, clinical efficacy has not been established.

Piperacillin can be inactivated *in vitro* by beta-lactamases produced by some strains of gram-negative and staphylococcal bacteria, however, it was found to be active against β-lactamase-producing gonococci.

In vitro testing of piperacillin combinations with gentamicin, tobramycin or amikacin shows a high incidence of synergistic action against strains of Pseudomonas, Serratia, Klebsiella, Proteus (indole-positive), Providencia and Staphylococcus species. Against other organisms, including strains of Enterobacter and Acinetobacter, partial synergy or indifference was noted. Overall, the data suggest that such combinations have clinical potential in the treatment of severe infections caused by these organisms.

Combinations of piperacillin with cephalosporin antibiotics may result in synergistic, additive, indifferent, or antagonistic effects. The effect appears to depend on the cephalosporin and the type of organism tested. Against strains of *Klebsiella*, *Escherichia coli*, *Acinetobacter*, *Proteus mirabilis*, *Salmonella*, enterococci, and *Staphylococcus aureus*, combinations of piperacillin with cefamandole or cefoxitin had synergistic, additive, or indifferent but no antagonistic effects. However, against *Pseudomonas*, *Enterobacter*, *Serratia*, and indole-positive *Proteus* strains, combinations of piperacillin with cefoxitin had a high frequency of antagonistic effects; combinations of piperacillin with cefamandole had additive or indifferent effects and a low frequency of antagonism.

Tests in mice reflect the *in vitro* observations. Piperacillin combinations with moxalactam, cefotaxime or cefoperazone have shown some limited *in vitro* synergy (18-25% of isolates tested) against *Pseudomonas aeruginosa* and *Serratia marcescens*.

The data indicate that piperacillin-cephalosporin combinations may have clinical advantages but that susceptibility tests should be conducted.

Susceptibility Tests:

The use of a 100 mcg piperacillin disc with susceptibility test methods which measure zone diameter gives an accurate estimation of *in vitro* susceptibility of organisms to piperacillin. The following standard procedure has been recommended for use with discs for testing antimicrobials*. Piperacillin 100 mcg discs should be used for the determination of the susceptibility of organisms to piperacillin. With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy.

*NCCLS approved standard: M2-A3 (Formerly ASM-2) Performance Standards for Antimicrobial Disc Susceptibility Tests, Third Edition.

A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (e.g. bile, urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy.

With the piperacillin disc, a zone of 18 mm or greater indicates susceptibility, zone sizes or 14 mm or less indicate resistance, and zone sizes of 15 to 17 mm indicate intermediate susceptibility. (TABLE 3)

Haemophilus, *Neisseria* and *Staphylococcus* species which give zones of ≥29 mm are susceptible; resistant strains give zones of ≤28 mm. The above interpretive criteria is based on the use of the standardized procedure. Antibiotic susceptibility testing requires carefully prescribed procedures. Susceptibility tests are biased to a considerable degree when different methods are used.

The standardized procedure requires the use of control organisms. The 100 mcg piperacillin disc should give zone diameters between 24 and 30 mm for *Escherichia coli* ATCC No. 25922 and between 25 and 33 mm for *Pseudomonas aeruginosa* ATCC No. 27853.

Dilution methods such as those described in the International Collaboration Study[1] and the NCCLS Approved Standard[2] have been used to determine susceptibility of the following organisms: *Enterobacteriaceae*, *Pseudomonas* species and *Acinetobacter* species are considered susceptible if the minimal inhibitory concentration of piperacillin (MIC) is no greater than 16 mcg/mL and are considered resistant if the MIC is greater than 128 mcg/mL.

Haemophilus and *Neisseria* species are considered susceptible if the MIC of piperacillin is less than or equal to 1 mcg/mL. *Staphylococcus* species are considered susceptible if the MIC of piperacillin is less than or equal to 0.12 mcg/mL. (See TABLE 4).

When anaerobic organisms are isolated from infection sites, it is recommended that other tests such as the modified Broth-Disk[3] method be used to determine the antibiotic susceptibility of these slowly-growing organisms.

TABLE 3
In Vitro Susceptibility as Measured with 100 mcg Piperacillin Discs

	PIPERACILLIN DISCS 100 mcg Zone Diameter (Millimeters)		
Bacteria	**Susceptible**	**Intermediate**	**Resistant**
All fast-growing bacteria except those listed below	≥18	15-17	≤14
Haemophilus spp. Neisseria spp. Staphylococcus spp.	≥29		≤28

When minimal inhibitory concentrations (MIC) are determined by standard dilution methods[4], the guidelines given in TABLE 4 are suggested.

TABLE 4
In Vitro Susceptibility as Measured by the Broth or Agar Dilution Method

	PIPERACILLIN: MIC (mcg/mL)		
Bacteria	**Susceptible**	**Moderately Susceptible**	**Resistant**
All bacteria except those listed below	≥16	32-64	≤128
Haemophilus spp.			
Neisseria spp.	≤1		≥1
Staphylococcus spp.	≤0.12		≥0.25

[1] Acta Pathologica et Microbiologica Scandinavica,Section B Suppl. 217, 1971.
[2] NCCLS Approved Standards: M7-A Methods for Dilution, Antimicrobial susceptibility tests for Bacteria
that grow Aerobically, December, 1985.

[3]Wilkins, T.D., and Thiel, T. Antimicrob. Agents Chemother. 3:350-356 (March) 1973.

[4] Acta Pathologica et Microbiologica Scandinavica, Section B Suppl. 217, 1971.

PHARMACOLOGY

Peak serum concentrations of piperacillin are attained approximately 30 minutes after intramuscular injection and immediately after intravenous injection or infusion. The serum half-life in healthy volunteers ranges from 36 minutes to 1 hour and 12 minutes. Serum levels after intravenous administration (see Table 5) and renal clearance do not show dose proportionality because of saturation of the renal secretory mechanism.

TABLE 5
PIPERACILLIN SERUM LEVELS IN HEALTHY ADULTS (mcg/mL)

Dose (g)	Route	2-3 min	30 min	1 hr	2 hrs	4 hrs	6 hrs
1.0	IM	-	21.9	14.6	9.0	2.4	0.9
2.0	IM	-	36.4	25.8	20.2	5.8	3.1
2.0	IV Bolus	305.1	66.8	40.2	20.1	2.6	1.4

4.0	IV Bolus	412.0	116.8	92.5	38.0	8.3	3.8
6.0	IV Bolus	775.0	325.0	207.6	89.8	33.2	8.1
4.0	IV Infusion (30 min.)	244.0	141	105	53	15.3 (4.5 hrs)	3.8 (6.5 hrs)
6.0	IV Infusion (30 min.)	353	229.0	149	73	22.2 (4.5 hrs)	15.8

Following a 30 minute infusion of 6 g every 6 hours, on the fourth day, mean peak serum concentrations were 420 mcg/mL.

Intramuscular Administration (See Table 5 above)
Piperacillin for Injection is rapidly absorbed after intramuscular injection. In healthy volunteers, the mean peak serum concentration occurs approximately 30 minutes after a single dose of 2 g and is about 36 mcg/mL.

The oral administration of 1 g probenecid before injection produces an increase in piperacillin peak serum level of about 30%. The area under the curve (AUC) is increased by approximately 60%.

The substitution of 0.5% lidocaine for Sterile Water as a diluent in a intramuscular pharmacokinetic study showed no significant difference in the area under the serum concentration curve, peak serum concentration or cumulative urine excretion of piperacillin. However, the serum half-lives were prolonged from 67 to 70 minutes at 3 g/day, 56 to 68 minutes at 4 g/day and 52 to 59 minutes at 6 g/day.

Intravenous Administration (see Table 5 above)
In healthy adult volunteers, mean serum levels immediately after a two to three minute intravenous injection of 2, 4 or 6 g were 305, 412, and 775 mcg/mL. Serum levels lack close proportionality.

Protein Binding:
Piperacillin binding to human serum proteins is 16%.

Distribution:
Piperacillin is widely distributed in human tissues and body fluids, including bone, prostate and heart and reaches high concentrations in bile (see TABLE 6). After a 4 gram bolus, maximum biliary concentrations averaged 3,205 mcg/mL. It penetrates into the cerebrospinal fluid in the presence of inflamed meninges. Because piperacillin is excreted by the biliary route (10-20%) as well as by the renal route, it can be used safely in appropriate dosages (see **DOSAGE AND ADMINISTRATION**) in patients with mild to severe renal impairment and can be used in treatment of hepato-biliary infections.

TABLE 6

DISTRIBUTION OF PIPERACILLIN IN ADULT HUMAN BODY TISSUES AND FLUIDS

Type of Tissue or Fluid	Tissue or Fluid Level (mcg/mL or mcg/g)	Time of Sampling (after dose)	Dose	Serum Level (mcg/mL)
TISSUES				
Bone, diseased	25.0	at surgery	300 mg/kg infusion	385.0
Cardiac muscle	113.5	10-20 min	100 mg/kg IV bolus	500.0
Gallbladder	26.0	1 hour	2 g IV	166.0
Intestinal wall (colon)	9.3	12 hr	2 g IV	12.3
Kidney, cortex	23.0-115.0	at surgery	4 g IV	NG*
Kidney, medulla	4.0-46.0	at surgery	4 g IV	NG*
Prostatic tissue	71.5	45 min	4 g IV bolus	185.0
Subcutaneous tissue	120.0	1 hr	4 g IV	140.0
Synovial tissue	135.0	NG*	300 mg/kg IV infus	385.0
Wound tissue	7.0	1 hr	2 g IV	30.0
FLUIDS				
Bile	3,247.0	1a hrs	4 g IV	86.7
Bronchial secretions	31.4	30-45 min	4 g IV bolus	196.3
Cerebrospinal fluid (meningitis patient)	6.7	4: hrs on day 2	74.3 mg/kg IV infus	7.5
Peritoneal fluid	35.5	2 hrs	50 mg/kg IV infus	46.6
Sputum	10.0	NG*	4-16 g/day IV or IM	>500.0
Urine	10,000.0	1 hr	2 g IM	36.4

* NOT GIVEN

Excretion:

As with other penicillins, piperacillin is eliminated primarily by glomerular filtration and tubular secretion; it is excreted rapidly as unchanged drug in high concentrations in the urine. Approximately 60% to 80% of the administered dose is excreted in the urine in the first 24 hours. Piperacillin urine concentrations, determined by microbioassay, were as high as 14,100 mcg/mL following a 6 g intravenous dose and 8,500 mcg/mL following a 4 g intravenous dose. These urine drug concentrations remained well above 1,000 mcg/mL throughout the dosing interval. The elimination half-life is increased two-fold in mild to moderate renal impairment and five-to-six-fold in severe impairment.

The mean elimination half-life of piperacillin in healthy adult volunteers is 54 minutes following administration of 2g and 63 minutes following 6g.

Miscellaneous:

Pharmacokinetic characteristics in patients with cystic fibrosis are somewhat different than in normal subjects in that, in the former, piperacillin has a shorter half-life, a decreased volume of distribution and an increase in clearance. These differences suggest the need for either increased dosages or shortened dosage intervals in patients with cystic fibrosis.

While piperacillin reduces platelet aggregation, these effects are less than those caused by ticarcillin or carbenicillin at equivalent therapeutic dosage.

There was no significant inactivation of amikacin, gentamicin or tobramycin in serum when the aminoglycoside was administered concomitantly with carbenicillin or piperacillin to subjects with normal renal function. In the urine, lowering of the concentration of tobramycin, and gentamicin to a lesser degree, by the presence of carbenicillin or piperacillin was observed. This possible inactivation effect was greater with carbenicillin than with piperacillin . No urinary inactivation of amikacin by either of these penicillins was observed. The clinical significance of these observations is unknown.

A follow-up study was conducted in patients with end-stage renal failure stabilized on chronic intermittent hemodialysis. No inactivation of piperacillin or carbenicillin in these patients was observed when gentamicin was administered concomitantly with either of these penicillins. Carbenicillin and piperacillin, however, inactivated gentamicin in these patients. Gentamicin was inactivated 4 times faster by carbenicillin than by piperacillin.

TOXICOLOGY

Acute Toxicity

The acute median lethal dose (LD_{50}) in rats was 2-3 g/kg (IV), 7-10 g/kg (IP), >10 g/kg (S.C.) in 6 and 12 week old rats, and 9 g/kg (S.C.) in 1 week old rats; in mice, the LD_{50} was 5 g/kg (IV), >10 g/kg (S.C.) and 10 g/kg (IP). Single intravenous doses of 2 and 4 g/kg were well tolerated in the dog with no changes in biochemical or hematological parameters. Signs of toxicity at 6 g/kg (IV) included emesis, diarrhea, salivation, and lacrimation. Slight to moderate increases in SGOT and SGPT values, white blood cell counts, and neutrophil-to-lymphocyte ratios were noted 1 day after dosing. A single 4 g/kg intravenous dose in the monkey produced similar biochemical and hematological changes and, in addition, moderate increase in lactic dehydrogenase and decreases in red blood cell counts.

Subacute and Chronic Toxicity

Rats given daily intraperitoneal doses of piperacillin (0.5-2 g/kg/day for 6 months and 1-4 g/kg/day for 1 month) showed no toxic effects except for reduced body weight gain in females at 4 g/kg/day only and in males at all dose levels.

Similar findings, plus evidence of renal damage, were seen in rats given ampicillin (2 g/kg/day for 1 month). In rats given 1, 2 or 4 g/kg twice daily intraperitoneally for 6 months, all showed an increase in lymphocytes at 4 and 6 months. At post-mortem all animals had unilateral hydronephrosis and some had urinary bladder urothelial hyperplasia, probably due to local irritation.

Dogs were given piperacillin for 1 month (up to 1 g/kg/day) IM (compared with ampicillin) and IV (alone and with gentamicin) and for 6 months (up to 2 g/kg/day IV). Transient increases in blood serum enzyme values, increases in kidney and liver weights, and mild local irritation at the injection site were seen in the 1-month IM study in both piperacillin- and ampicillin-treated dogs. No other toxic effects were seen in the adult dog studies and there was no synergistic toxicity when piperacillin was combined with gentamicin.

Special Toxicity Studies

Daily intravenous administration of 0.5-1 g/kg/day for 1 month in the rat did not cause loss of pinna reflex (as a measurement of ototoxic effect) at any frequency from 200-20,000 Hz.

In 4 dogs, daily administration of 2 g/kg intravenously for 1 month resulted in no drug-induced changes in liver or kidney on electron microscopic examination. The same animals showed no eye abnormalities observable by gross examination or direct ophthalmoscopy.

Reproduction and Teratology

Subcutaneous or intravenous administration of piperacillin sodium (0.5, 1 or 2 g/kg) to mice prior to mating (and in females extending into early gestation), during the period of organogenesis, or during late gestation and through the lactation period, had no adverse effect on reproductive success or the development of offspring. Survival rates, weaning rates and body weights were higher in offspring of treated dams than controls.

In rats, with the possible exception of a slight decrease in the survival rate of pups of high-dose dams, subcutaneous administration of 0.25-1 g/kg of piperacillin sodium during the period of organogenesis had no adverse effects on reproductive success or the development of offspring.

Intraperitoneal doses of 0.5, 1.0 and 2.0 g/kg/day, given to rats (males for 9 weeks prior to mating and females for 2 weeks prior to mating and until the offsprings were weaned) had no adverse effects except at the 2 g/kg/day dose level where longer precoital time and a lower pregnancy rate were noted; no firm conclusions can be drawn. In the offspring of these animals, no adverse effects regarding early neonatal development, fertility and reproductive performance attributable to treatment of the parents with piperacillin sodium were demonstrated.

In rabbit teratology range finding studies, intravenous doses of 0.25 to 1 g/kg/day of piperacillin sodium from day 6 to 18 of gestation produced marked decreases in food intake and body weight. Maternal mortality and intrauterine deaths were high in all treatment groups; however, fetuses which did survive had no external morphologic abnormalities. Similar results were seen in dams dosed with 1 g/kg/day (single dose or 0.5 g/kg b.i.d.) from day 6 to 8 of gestation.

Mutagenicity

Piperacillin was non-mutagenic in in vivo cytogenetics, Ames Test, Host-Mediated (mouse) assay, Induction of Unscheduled DNA Synthesis and Dominant Lethal test systems.

Local Irritation

An injection of 0.05 mL of 250-500 mg/mL piperacillin given intracutaneously in the rat produced local reaction similar to ampicillin and carbenicillin.

In the rabbit eye, a single 0.1 mL instillation of 500 mg/mL piperacillin produced no changes at 24 or 72 hours. Single or multiple intramuscular injections of piperacillin 25, 35 or 40% in Sterile Water were similar to or less irritating than carbenicillin in rabbits.

Single or multiple injections of piperacillin 25 or 40% solutions in either saline (with and without lidocaine) or Sterile Water (with and without lidocaine) were generally well tolerated, though aqueous solutions were better tolerated than saline solutions.

Single injections of piperacillin 40% solution in saline or Sterile Water solution with lidocaine were better tolerated than 2.5% solutions of tetracycline HCl. In another rabbit study 0.05 mL of a 200 mg/mL solution was injected into an occluded auricular vein for 3 minutes, three times daily for three days. Piperacillin was somewhat less irritating than the carbenicillin or ampicillin controls when incidence, onset or length of thrombus were compared.

Effects on Blood

Concentrations up to 500 mg/mL piperacillin sodium did not produce hemolysis of rabbit erythrocytes *in vitro*; using human erythrocytes hemolysis was produced at concentrations higher than 240 mg/mL. Ampicillin and carbenicillin produced hemolysis at concentrations of 200 mg/mL and higher with human erythrocytes.

Bleeding time in mice was unchanged at IV doses of 250 mg/kg piperacillin sodium, but increased at doses of 500 and 1000 mg/kg. Increases were seen with 1000 mg/kg of ampicillin and carbenicillin.

Neither piperacillin sodium, ampicillin nor carbenicillin affected rabbit blood prothrombin and partial thromboplastin time *in vitro* at 10^{-5} to 10^{-3} g/mL; all compounds prolonged PT and PTT at 10^{-2} g/mL.

IV doses of 0.5 or 1.0 g/kg of the same compounds did not affect PT but decreased PTT.

Concentrations of piperacillin sodium, ampicillin and carbenicillin from 10^{-5} to 10^{-3} g/mL did not affect platelet aggregation induced by adenosine diphosphate or collagen; all compounds inhibited aggregation at a concentration of 10^{-2} g/mL.

Possible Immune Responses

No skin sensitization occurred with doses of 1, 5 and 10 mg/ 0.5 mL of piperacillin sodium in guinea pigs. No signs of anaphylaxis were seen in guinea pigs at doses of 3 to 150 mg/kg. Protein conjugates of piperacillin sodium produced only slightly positive Arthus reactions after subcutaneous injection in rabbits. Cross reactivity (passive cutaneous anaphylaxis) of piperacillin sodium with ampicillin or penicillin G was weak, displaying 1/8 and 1/16 of the titers from the homologous antigen-antibody systems.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Piperacillin for Injection
(Piperacillin Sodium)

Read this carefully before you start taking Piperacillin for Injection and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Piperacillin for Injection.

What is Piperacillin for Injection used for?
Piperacillin for Injection is used to treat infections.

Antibacterial drugs like Piperacillin for Injection treat only bacterial infections. They do not treat viral infections such as the common cold.

How does Piperacillin for Injection work?
Piperacillin for Injection is an antibiotic. It kills bacteria that other antibiotics may not treat effectively. You should start to feel better after 48 to 72 hours of receiving Piperacillin for Injection.

What are the ingredients in Piperacillin for Injection?
Medicinal ingredient: Piperacillin Sodium
Non-medicinal ingredient: None

Piperacillin for Injection comes in the following dosage forms:
2 g, 3g and 4 g of piperacillin per vial

Do not use Piperacillin for Injection if:

- you are allergic to Piperacillin Sodium or any of the ingredients that are in Piperacillin for Injection. See "What are the ingredients in Piperacillin for Injection", above.
- you are sensitive to certain numbing agents that may have been used in the preparation with your injection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Piperacillin for Injection. Talk about any health conditions or problems you may have, including if you:

- have sensitivity to other antibiotics like penicillins or cephalosorins
- are known to have a bleeding problem
- have cystic fibrosis
- suspect that you may have syphilis or mononucleosis (mono)
- have kidney disease

- have liver disease

Other warnings you should know about:

- Piperacillin for Injection may cause seizures, shaking or convulsions.
- Piperacillin for Injection contains sodium and patients on restricted salt intake may need blood test monitoring.
- Tell your healthcare professional if you are a nursing mother. Piperacillin for Injection is excreted in human milk.
- Tell your healthcare professional if you are pregnant or plan to become pregnant. It is not known if Piperacillin for Injection will harm your unborn baby.
- Inflammation of the intestines (gut) has also been reported from using all antibiotics including Piperacillin for Injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Piperacillin for Injection:

- Other antiobiotics and aminoglycosides (drugs used to treat infections such as penicillin, ampicillin, amoxicillin, probenecid and gentamicin)
- Drugs that block the activity of the muscles (muscle relaxants such as vecuronium)

How to take Piperacillin for Injection:

- Although you may feel better early in treatment, Piperacillin for Injection should be used exactly as directed.
- Misuse or overuse of Piperacillin for Injection could lead to the growth of bacteria that will not be killed by Piperacillin for Injection (resistance). This means that Piperacillin for Injection may not work for you in the future.
- Do not share your medicine.

Adult Dose:

The maximum daily dose is 24 g/day.

Injection in the muscle: maximum of 2 g per injection site
Injection in the vein: slowly over a 3 to 5 minute period
Injection in the vein: 20 to 40 minutes (intermittent infusion: 30 minutes to 2 hour)

Dosages in infants and children under 12 years of age have not been established.

Overdose:

If you think you have taken too much Piperacillin for Injection, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Piperacillin for Injection?

These are not all the possible side effects you may feel when taking Piperacillin for Injection. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Redness, swelling or bruising at the injection site
- Blood clot in vein
- Fever
- Allergic reaction
- Rash, redness or itching over body or other skin conditions or skin discoloration
- Diarrhea
- Headache
- Dizziness
- Fatigue
- Convulsions (high doses)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Piperacillin for Injection vials should be stored at between 15 and 30°C, protected from light. Keep out of reach and sight of children.

If you want more information about Piperacillin for Injection:
Talk to your healthcare professional.
Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

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Last Revised: March 8, 2018