Product Information
PipTaz-AFT

AFT Pharmaceuticals Ltd.

PRODUCT NAME

PipTaz-AFT Powder for Solution for Injection 4.5g/vial (Piperacillin 4g and Tazobactam 500mg)

PRODUCT DESCRIPTION

PipTaz-AFT is a sterile, white or off-white lyophilized powder containing piperacillin sodium equivalent to piperacillin 4g and tazobactam sodium equivalent to tazobactam 500mg, packed in a clear, colourless, transparent 50ml Type 1 glass vial. Each vial contains 214mg sodium. This product contains excipients such as Sodium Bicarbonate and Water for Injection.

It is highly hygroscopic, and soluble in water.

The reconstituted solution of PipTaz-AFT is clear, colourless or off-white depending on the type and concentration of diluents used.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties Pharmacotherapeutic Group

Antibacterials for systemic use, combinations of penicillins including β-lactamase inhibitors; ATC code: J01C R05.

Mode of Action:

PipTaz-AFT (sterile piperacillin sodium/tazobactam sodium) is an injectable antibacterial combination consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration. Thus, piperacillin/tazobactam combines the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. Piperacillin and other β-lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible organisms by interacting with penicillin-binding proteins (PBPs), the bacterial enzymes that carry out this reaction. In vitro, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.

Piperacillin has reduced activity against bacteria harboring certain β-lactamase enzymes, which chemically inactivate piperacillin and other β-lactam antibiotics. Tazobactam sodium, which has very little intrinsic antimicrobial activity, due to its low affinity for PBPs, can restore or enhance the activity of piperacillin against many of these resistant organisms. Tazobactam is a potent inhibitor of many class A β-lactamases (penicillinases, cephalosporinases and extended spectrum enzymes). It has variable activity against class A carbapenemases and class D β-lactamases. It is not active against most class C cephalosporinases and inactive against Class B metallo-β-lactamases.

Two features of piperacillin/tazobactam lead to increased activity against some organisms harboring β- lactamases that, when tested as enzyme preparations, are less inhibited by tazobactam and other inhibitors: tazobactam does not induce chromosomally mediated β-lactamases at tazobactam levels achieved with the recommended dosing regimen and piperacillin is relatively refractory to the action of some β-lactamases.

Like other β-lactam antibiotics, piperacillin, with or without tazobactam, demonstrates time-dependent bactericidal activity against susceptible organisms.

Mechanism of Resistance:

There are three major mechanisms of resistance to β-lactam antibiotics: changes in the target PBPs resulting in reduced affinity for the antibiotics, destruction of the antibiotics by bacterial β-lactamases, and low intracellular antibiotic levels due to reduced uptake or active efflux of the antibiotics.

In gram-positive bacteria, changes in PBPs are the primary mechanism of resistance to β-lactam antibiotics, including piperacillin/tazobactam. This mechanism is responsible for methicillin resistance in staphylococci and penicillin resistance in Streptococcus pneumoniae and viridans group streptococci. Resistance caused by changes in PBPs also occurs in fastidious gram-negative species, such as Haemophilus influenzae and Neisseria gonorrhoeae. Piperacillin/tazobactam is not active against strains in which resistance to β-lactam antibiotics is determined by altered PBPs. As indicated above, there are some β-lactamases that are not inhibited by tazobactam.

Methodology for Determining the *In Vitro* Susceptibility of Bacteria to Piperacillin/Tazobactam:

Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (minimal inhibitory concentration, [MIC], determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide susceptibility interpretive criteria for some bacterial species based on these methods. It should be noted that for the disk diffusion method, CLSI and EUCAST use disks with different drug contents.

The CLSI interpretive criteria for susceptibility testing of piperacillin/tazobactam are listed in the following table:

Pathogen	Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]			Disk[b] Diffusion Inhibition Zone (mm Diameter)		
	S	I	R	S	I	R
Enterobacteriaceae and *Acinetobacter baumannii*	≤16	32 - 64	≥128	≥21	18 - 20	≤17
Pseudomonas aeruginosa	≤16	32 - 64	≥128	≥21	15 - 20	≤14
Certain other non-fastidious gram-negative bacilli[c]	-	-	-	≥21	18 - 20	≤17
Haemophilus influenzae	≤1	-	≥2	≥21	-	-
Staphylococcus aureus	≤8	-	≥16	≥18	-	≤17
Bacteroides fragilis group[d]	≤32	64	≥128	-	-	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement*. CLSI document M100-S22. CLSI, Wayne, PA, 2012. S = Susceptible. I = Intermediate. R = Resistant.

[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.

[b] CLSI interpretive criteria are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.

[c] Refer to CLSI Document M100-S22 Table 2B-5 for the list of organisms included.

[d] With the exception of *Bacteroides fragilis* itself, MICs are determined by agar dilution only.

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant. Organisms and quality control ranges for piperacillin/tazobactam to be utilized with CLSI methodology and susceptibility test interpretive criteria are listed in the following table:

Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with CLSI Susceptibility Test Interpretive Criteria		
Quality Control Strain	**Minimal Inhibitory Concentration (mg/L of piperacillin)**	**Disk Diffusion Inhibition Zone (mm Diameter)**
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 ATCC 49247	0.06 - 0.5	33-38
Staphylococcus aureus ATCC 29213	0.25 - 2	-
Staphylococcus aureus ATCC 25923	-	27 - 36
Bacteroides fragilis ATCC 25285	0.12 - 0.5[a]	-
Bacteroides thetaiotaomicron ATCC 29741	4 - 16[a]	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement*. CLSI document M100-S22. CLSI, Wayne, PA, 2012.

[a] Agar dilution only.

EUCAST has also established clinical breakpoints for piperacillin/tazobactam against some organisms. Like CLSI, the EUCAST MIC susceptibility criteria are based on a fixed concentration of 4 mg/L of tazobactam. However, for inhibition zone determination, the disks contain 30 µg of piperacillin and 6 µg of tazobactam. The EUCAST rationale document for piperacillin/tazobactam states that breakpoints for Pseudomonas aeruginosa apply to dosages of 4 g, 4 times daily, whereas the breakpoints for other organisms are based on 4 g, 3 times daily.

The EUCAST breakpoints for piperacillin/tazobactam are listed in the following table:

EUCAST Susceptibility Interpretive Criteria for Piperacillin/Tazobactam				(mm
Pathogen	**Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]**			
	S	**R**	**S**	**R**
Enterobacteriaceae	≤8	>16	≥20	<17
Pseudomonas aeruginosa	≤16	>16	≥19	<19
Gram-positive anaerobes	≤8	>16	-	-
Gram-negative anaerobes	≤8	>16	-	-
Non-species related	≤4	>16	-	-

Sources:
EUCAST Clinical Breakpoint Table v. 2.0, 1 January 2012.
Piperacillin-tazobactam: Rationale for the EUCAST clinical breakpoints, version 1.0, 22 November 2010. S = Susceptible. R = Resistant.

[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.

[b] EUCAST interpretive criteria are based on disks containing 30 µg of piperacillin and 6 µg of tazobactam.

Per EUCAST, for species without piperacillin/tazobactam breakpoints, susceptibility in staphylococci is inferred from cefoxitin/oxacillin susceptibility. For groups A, B, C and G streptococci and *Streptococcus pneumoniae*, susceptibility is inferred from benzylpenicillin susceptibility. For other streptococci, enterococci, and β-lactamase-negative *Haemophilus influenzae*, susceptibility is inferred from amoxicillin-clavulanate susceptibility. There are no EUCAST breakpoints for *Acinetobacter*. The EUCAST rationale document for piperacillin/tazobactam states that in endocarditis caused by streptococci other than groups A, B, C and G and *S. pneumoniae*, national or international guidelines should be referred to.

Quality control ranges for EUCAST susceptibility breakpoints are listed in the following table.

Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with EUCAST Susceptibility Test Interpretive Criteria		
Quality Control Strain	**Minimal Inhibitory Concentration (mg/L of piperacillin)**	**Disk Diffusion Inhibition Zone (mm Diameter)**
Escherichia coli ATCC 25922	1 – 4	21 - 27
Pseudomonas aeruginosa ATCC 27853	1 – 8	23 - 29

Source: EUCAST recommended strains for internal quality control. Version 2.0, 1 January 2012.

MICs are determined using a fixed concentration of 4mg/L Tazobactam.

PipTaz-AFT is highly active against piperacillin-sensitive micro-organisms as well as many β-lactamase producing, piperacillin-resistant micro-organisms.

Gram-negative bacteria: most plasmid mediated β-lactamase producing and non-β-lactamase producing strains of *Escherichia coli, Shigella spp., Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella spp. (*including *M. catarrhalis), Haemophilus spp. (*including *H. influenzae, H. parainfluenzae), Pasteurella multocida, Yersinia spp., Campylobacter spp., Gardnerella vaginalis.* Many chromosomally mediated β-lactamase producing and non-β- lactamase producing strains of *Enterobacter* spp. (including *E. cloacae, E. aerogenes), Citrobacter spp.* (including *C. freundii, C. diversus), Providencia spp., Morganella morganii, Serratia spp.* (including *S. marcescens, S. liquefaciens), Pseudomonas aeruginosa and other Pseudomonas spp.* (including *P. cepacia, P. fluorescens), Xanthomonas maltophilia, Acinetobacter spp.*

Gram-positive bacteria: β-lactamase producing and non-β-lactamase producing strains of streptococci (*S. pneumoniae, S. pyogenes, S. bovis, S. agalactiae, S. viridans*, Group C, Group G), enterococci (*E. faecalis*), *Staphylococcus aureus* (not methicillin-resistant S. aureus), *S. saprophyticus, S. epidermidis* (coagulase-negative staphylococci), corynebacteria, *Listeria monocytogenes, Nocardia* spp.

Anaerobic bacteria: β-lactamase producing and non-β-lactamase producing anaerobes, such as *Bacteroides* spp. (including *B. bivius, B. disiens, B. capillosus, B. melaninogenicus, B. oralis*), the *Bacteroides fragilis* group (including *B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. thetaiotaomicron, B. uniformis, B. asaccharolyticus*), as well as *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium* group, *Clostridia* spp. (including *C. difficile, C. perfringens*), *Veillonella* spp., and *Actinomyces* spp.

Pharmacokinetic properties

Adults

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of piperacillin/tazobactam. Piperacillin plasma concentrations, following a 30-minute infusion of piperacillin/tazobactam, 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 PipTaz-AFT (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 piperacillin/tazobactam 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 piperacillin/tazobactam were administered via 30-minute infusions every 6 hours. Steady-state plasma concentrations after 30-minute infusions every 6 hours are provided in the table below.

STEADY-STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS								
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	PIPERACILLIN Plasma Concentrations** (µg/mL)						AUC** (µg•hr/mL)
		30 mins	1 hour	2 hours	3 hours	4 hours	6 hours	AUC0-6
2.25g	8	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14)[b]	131 (14)
3.375g	6	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1.0 (10)	242 (10)
4.5g	8	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

STEADY-STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS								
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	TAZOBACTAM Plasma Concentrations** (µg/mL)						AUC** (µg•hr/mL)
		30 mins	1 hour	2 hours	3 hours	4 hours	6 hours	AUC0-6
2.25g	8	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6)[c]	<0.5	16.0 (21)
3.375g	6	24.2 (14)	10.7 (7)	4.0 (18)	1.4 (21)	0.7 (16)[b]	<0.5	25.0 (8)
4.5g	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

- **Distribution**

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, bile and bone. 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.

- **Metabolism**

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that has been found to be microbiologically inactive.

- **Elimination**

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 appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

Following administration of single or multiple piperacillin/tazobactam 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. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

There are no significant changes in the pharmacokinetics of piperacillin due to tazobactam. Piperacillin appears to reduce the rate of elimination of tazobactam.

- **Special Populations**

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

The half-lives of piperacillin and tazobactam increase with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 mL/min compared to patients with normal renal function.

Hemodialysis removes 30% to 50% of piperacillin/tazobactam 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 18% of the tazobactam dose removed as the tazobactam metabolite.

Preclinical safety data

- **Carcinogenicity**

Carcinogenicity studies have not been conducted with piperacillin, tazobactam, or the combination.

- **Mutagenicity**

Piperacillin/tazobactam was negative in microbial mutagenicity assays. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell hypoxanthine phosphoribosyltransferase [HPRT]) assay. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay. In vivo, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed intravenously.

Piperacillin was negative in microbial mutagenicity assays. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin. Piperacillin was negative in the UDS test. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay. In vivo, piperacillin did not induce chromosomal aberrations in mice dosed intravenously.

Tazobactam was negative in microbial mutagenicity assays. Tazobactam was negative in the UDS test. Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay. In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive. Tazobactam was negative in a cell (BALB/c-3T3) transformation assay. In an in vitro cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative. In vivo, tazobactam did not induce chromosomal aberrations in rats dosed intravenously.

- **Reproductive Toxicity**

In embryo-fetal development studies there was no evidence of teratogenicity following intravenous administration of tazobactam or the piperacillin/tazobactam combination; however, in rats there were slight reductions in fetal body weight at maternally toxic doses.

Intraperitoneal administration of piperacillin/tazobactam was associated with slight reductions in litter size and an increased incidence of minor skeletal anomalies (delays in bone ossification) at doses that produced maternal toxicity. Peri-/post-natal development was impaired (reduced pup weights, increase in still birth, increase in pup mortality) concurrent with maternal toxicity.

Impairment of Fertility

Reproduction studies in rats revealed no evidence of impaired fertility due to tazobactam, or piperacillin/tazobactam when administered intraperitoneally.

INDICATIONS

PipTaz-AFT is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Lower respiratory tract infections; urinary tract infections (complicated and uncomplicated); intra-abdominal infections; skin and skin structure infections; bacterial septicemia.

Polymicrobial infections: PipTaz-AFT is indicated for polymicrobial infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, lower respiratory tract).

PipTaz-AFT, in combination with an aminoglycoside, is indicated for bacterial infections in neutropenic adults or children.

- **Children Under the Age of 12 Years**

In hospitalized children aged 2 to 12 years, PipTaz-AFT is indicated for the treatment of intra-abdominal infections including appendicitis complicated by rupture or abscess, peritonitis, and biliary infections. It has not been evaluated in this indication for pediatric patients below the age of 2 years.

Whilst PipTaz-AFT is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amendable to PipTaz-AFT treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and β-lactamase producing organisms susceptible to PipTaz-AFT should not require the addition of another antibiotic.

PipTaz-AFT is particularly useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests because of its broad spectrum of activity.

PipTaz-AFT acts synergistically with aminoglycosides against certain strains of Pseudomonas aeruginosa. Combined therapy has been successful, especially in patients with impaired host defences. Both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted if necessary.

DOSAGE AND ADMINISTRATION

- **Dosage**

Neutropenic patients with signs of infection (e.g. fever) should receive immediate empirical antibiotic therapy before laboratory results are available.

- **Adults and children over 12 years**

The usual dosage for adults and children over 12 years with normal renal function is 4.5g PipTaz-AFT given every eight hours. The total daily dose depends on the severity and localization of the infection and can vary from 2.25g to 4.5g PipTaz-AFT administered every six or eight hours.

In neutropenia, the recommended dose is 4.5g PipTaz-AFT given every six hours in combination with an aminoglycoside.

- **Children under the age of 12 years**

PipTaz-AFT is only recommended for the treatment of children with neutropenia.

For children weighing over 50 kg, follow adult dosing guidance, including the aminoglycoside. For children with normal renal function
and weighing less than 50kg, the dose should be adjusted to 90mg/kg (80mg piperacillin/10mg tazobactam) administered every six hours in combination with an aminoglycoside.

Until further experience is available, PipTaz-AFT should not be used in children who do not have neutropenia.

- **Hospitalized children with intra-abdominal infection**

For children aged 2 to 12 years, weighing up to 40kg, and with normal renal function, the recommended dose is 112.5mg/kg (100mg piperacillin/12.5mg tazobactam) every 8 hours. For children aged 2 to 12 years, weighing over 40kg, and with normal renal function, follow the adult dosing guidance, i.e. 4.5g (4g piperacillin/0.5g tazobactam) every 8 hours. The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

- **Elderly**

PipTaz-AFT may be used at the same dose levels as adults except in cases of renal impairment (see below):

- **Renal insufficiency in adults and children weighing >50 kg**

In adults and children weighing >50 kg with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS AND CHILDREN >50 KG WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
20-80	12 g/1.5 g/day Divided Doses 4 g/500 mg q 8H
<20	8g/1g/day Divided Doses 4 g/500 mg q 12H

For patients on hemodialysis, the maximum daily dose is 8 g/1 g PipTaz-AFT. In addition, because hemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2 g/250 mg PipTaz-AFT should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of PipTaz-AFT will provide additional guidance for adjusting dosage.

- **Renal insufficiency in adults and children weighing <50 kg**

In adults and children weighing <50 kg with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

INTRAVENOUS DOSAGE SCHEDULE FOR CHILDREN <50KG WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
40-80	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 6H
20-40	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 8H
<20	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 12H

For children weighing <50 kg on hemodialysis, the recommended dose is 45 mg/kg q 8H.

The pharmacokinetics of PipTaz-AFT have not been studied in pediatric patients with renal impairment. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval dose should be adjusted accordingly. In patients with renal insufficiency or hemodialysis patients, intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment.

- **Duration of therapy**

Therapy is recommended for a minimum of 5 days and maximum of 14 days, considering that dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms or fever.

- **Administration**

PipTaz-AFT must be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (e.g., over 20-30 minutes).

Whenever PipTaz-AFT is used concurrently with another antibiotic, especially an aminoglycoside, the drug must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility.

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

CONTRAINDICATION

Hypersensitivity to any of the β-lactams (including penicillins and cephalosporins) or to β-lactamase inhibitors.

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic/ anaphylactoid (including shock)) reactions have been reported in patients on penicillin/ cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/ cephalosporin hypersensitivity who have experienced severe reactions when treated with either a penicillin or cephalosporin. Past history of a severe allergic reaction to penicillin/ cephalosporin is a contraindication to the use of PipTaz-AFT. Before initiating therapy with any penicillin/ cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, PipTaz- AFT use should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation should also be administered as indicated.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including piperacillin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

PipTaz-AFT may cause serious cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustolosis. If patients develop a skin rash they should be monitored closely and PipTaz-AFT discontinued if lesions progress.

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of haemopoietic function should be performed.

Use with caution in the following circumstances:

Bleeding manifestations have occurred in some patients receiving piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests, e.g. clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause 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 are given intravenously.

Repeated use of lignocaine as a solvent should be avoided in patients with severe liver disease or decreased hepatic blood flow, due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

Combined administration of beta-lactamase inhibitors and beta-lactam antibiotics may be associated with a slightly increased risk of hepatic adverse reactions. The incidence of increased liver enzymes in patients treated with piperacillin/tazobactam was slightly higher than has been reported previously with the use of piperacillin alone. The potential for increased hepatic adverse reactions should be borne in mind when using piperacillin/tazobactam.

Check the following before use:

Periodic assessment of organ system functions, including renal, hepatic and haemopoietic, during prolonged therapy (greater than or equal to 21 days), is advisable.

For patients with renal impairment and/or hepatic insufficiency, measurement of serum levels of piperacillin will provide guidance for adjusting dosage.

Due to its potential nephrotoxicity, piperacillin / tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment (see DOSAGE AND ADMINISTRATION).

Periodic electrolyte determinations should be made in patients with low potassium reserves and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Because of its poor penetration into the CSF, piperacillin is not advised in the treatment of meningitis and brain abscess.

Antimicrobials used in high doses for short periods to treat gonorrhoea may mask or delay symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhoea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serological tests should be made for a minimum of four months.

Impaired renal function

See Check the following before use, above.

Impaired hepatic function

See Check the following before use, above.

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

Pregnancy and lactation

Category B1

Adequate human studies on the use of Piperacillin/tazobactam during pregnancy are not available.

Limited studies with piperacillin alone in rats and mice revealed no teratogenic effects or harm to the foetus. Studies with tazobactam (doses up to 3,000mg/kg intravenously) or tazobactam and piperacillin (doses up to 750mg/kg and 3,000mg/kg intravenously) in mice showed no evidence of teratogenicity or harm to the foetus. Studies in rats at these dose levels showed no evidence of teratogenicity although maternal toxicity, in the form of decreased weight gain, was noted at the dose levels tested. Piperacillin has been found to cross the placenta in rats. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Use in lactation

Adequate clinical studies on the use of Piperacillin/tazobactam during pregnancy are not available. Piperacillin is excreted in low concentrations in milk. In animal studies, both piperacillin and tazobactam were excreted in the milk of lactating rates. Women who are breastfeeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed.

Other

Carcinogenicity, mutagenicity, impairment of fertility

Long-term carcinogenicity studies of Piperacillin/tazobactam in animals have not been performed. Mutagenicity studies with piperacillin and tazobactam showed no evidence of genotoxicity in assays for chromosomal and DNA damage. One assay for gene mutations (mouse lymphoma assay) was weakly positive at tazobactam and piperacillin concentrations greater than or equal to 3,200 microgram/mL and 2,500 microgram/mL, respectively. Piperacillin and tazobactam did not affect the fertility of male or female rats.

Use in children

Safety and efficacy of the use of PipTaz-AFT in children under the age of two years have not yet been established.

SIDE EFFECTS AND ADVERSE REACTIONS

Adverse Drug Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (cannot be estimated from available data)
Infections and infestations		candida infection*		pseudomembranous colitis	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*	leukopenia	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*, eosinophilia*
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Metabolism and nutrition disorders			hypokalemia		
Psychiatric disorders		insomnia			
Nervous system disorders		headache			
Vascular disorders			hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia*
Gastrointestinal disorders	diarrhea	abdominal pain, vomiting, constipation, nausea, dyspepsia		stomatitis	
Hepatobiliary disorders					hepatitis*, jaundice
Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculo-papular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous, purpura
Musculoskeletal connective tissue and bone disorders			arthralgia, myalgia		
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*
General disorders and administration site conditions		pyrexia, injection site reaction	chills		
Investigations		alanine aminotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gamma-glutamyltransferase increased

*ADR identified post-marketing.

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

DRUG INTERACTIONS

Concurrent administration of probenecid and piperacillin/tazobactam produced a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of neither drug are affected. No kinetic interactions are found between piperacillin/tazobactam and vancomycin. However, a limited number of retrospective studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone.

Concurrent administration of piperacillin and tobramycin in patients with severe renal dysfunction (i.e. chronic haemodialysis patients) has been reported to reduce the elimination half-life and significantly increase the total body clearance of tobramycin.

The alteration of tobramycin pharmacokinetics in patients with mild to moderate renal dysfunction who are taking piperacillin concomitantly is unknown. However, reports suggest that the aminoglycoside inactivation in patients concomitantly taking an aminoglycoside with broad spectrum beta-lactam penicillin is only clinically significant in patients with severe renal dysfunction.

The inactivation of aminoglycosides in the presence of penicillin class drugs has been recognised. It has been postulated that penicillin/ aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity.

Piperacillin, when used concomitantly with vecuronium, has been implicated in the prolongation of the neuromuscular blockade of vecuronium. PipTaz-AFT 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-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid drug toxicity.

If piperacillin/tazobactam is used concurrently with another antibiotic, especially an aminoglycoside, the drugs must not be mixed in intravenous solutions or administered concurrently, due to physical incompatibility.

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

Effects on laboratory tests

As with other penicillins, the administration of piperacillin/ tazobactam may result in a false positive reaction for glucose in the urine using a copper reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

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

SYMPTOM OF OVERDOSE AND TREATMENT

Symptoms

There have been post-marketing reports of overdose with piperacillin/ tazobactam. The majority of those events experienced, including nausea, vomiting and diarrhoea, 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

No specific antidote is known. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin. In cases of motor excitability or convulsions, anticonvulsive agents (e.g. diazepam or barbiturates) may be indicated. In cases of anaphylactic reactions, the usual countermeasures are to be initiated (adrenaline, antihistamines, corticosteroids and, if required, oxygen and airway management).

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis. For further detailed information, advice may be sought from the Poisons Information Centre

INCOMPATIBILITY

Piperacillin/tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. Whenever piperacillin/ tazobactam is used concurrently with another antibiotic, the drugs must be administered separately.

Because of chemical instability, piperacillin/tazobactam should not be used with lactated Ringer's solution, solutions containing only sodium bicarbonate or having a pH in the basic range.

Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

STORAGE AND SHELF LIFE

Shelf life: 2 years (24 months) from the date of manufacture. PipTaz-AFT should be stored below 30°C.

PipTaz-AFT must be reconstituted with not less than 20mL sterile water for injections, dextrose 5% or sodium chloride injection prior to use.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2 °C- 8 °C for not more than 24 hours.

PRODUCT PRESENTATION

PipTaz-AFT is available in packs containing 1 or 10 vials. Each vial contains piperacillin sodium equivalent to piperacillin 4g and tazobactam sodium equivalent to tazobactam 500mg. Each vial also contains 214mg sodium.

PRODUCT OWNER AND MANUFACTURER

Product Owner:

AFT Pharmaceuticals Ltd.,
Level 1, Nielsen Building, 129 Hurstmere Road, Takapuna, Auckland 0622, New Zealand

Manufacturer:

Shandong Anxin Pharmaceutical Co., Ltd.
No. 849 Dongjia Town, Licheng District, Jinan, 250105 Shandong, China

DATE OF REVISION

May 202005-V1