For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TORBAC
(Piperacillin and Tazobactam for Injection U.S.P.)

COMPOSITION
Each vial contains:
Sterile Piperacillin Sodium U.S.P. equivalent to Piperacillin 4 gm
Sterile Tazobactam Sodium equivalent to Tazobactam 0.5 gm

INDICATIONS
In the treatment of lower RTI/UTI/intra-abdominal infections, skin and skin structure infections, bacterial septicaemia polymicrobic infection.

POSOLOGY AND METHOD OF ADMINISTRATION
Piperacillin/tazobactam should be administered by intravenous infusion over 30 minutes. The usual total daily dose of Piperacillin/tazobactam for adults is 3.375 g every six hours totalling 13.5 g (12 g piperacillin sodium/1.5 g tazobactam sodium).
Initial presumptive treatment of patients with nosocomial pneumonia should start with piperacillin/tazobactam at a dosage of 4.5 g every six hours plus an aminoglycoside, totalling 18.0 g (16.0 g piperacillin sodium/2.0 g tazobactam sodium). Treatment with the aminoglycoside should be continued in patients from whom Pseudomonas aeruginosa is isolated. If Pseudomonas aeruginosa is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Renal Insufficiency
In patients with renal insufficiency, the intravenous dose of Piperacillin/ tazobactam should be adjusted to the degree of actual renal function impairment.
In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Piperacillin/tazobactam for patients with renal insufficiency are as follows:
Recommended Dosing of Piperacillin/tazobactam in Patients with Normal Renal Function and Renal Insufficiency (As total grams piperacillin/tazobactam)

Renal Function (Creatinine Clearance, mL/min)	**All Indications (except Nosocomial Pneumonia**	**Nosocomial Pneumonia**
>40	3.375 q 6 h	4.5 q 6 h
20-40 *	2.25 q 6 h	3.375 q 6 h
<20 *	2.25 q 8 h	2.25 q 6 h
Hemodialysis**	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h
* Creatinine clearance for patients not receiving hemodialysis ** 0.75 g should be administered following each hemodialysis session on hemodialysis days		

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g Piperacillin/tazobactam should be administered following each dialysis period on

hemodialysis days. No additional dosage of Piperacillin/tazobactam is necessary for CAPD patients.

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

DIRECTIONS FOR RECONSTITUTION AND DILUTION FOR USE
Each vial of 4.5 g should be reconstituted with 20ml of sterile water for injection. Shake well until dissolved. Administer by infusion over a period of at least 30 minutes.

STABILITY FOLLOWING RECONSTITUTION
When reconstituted as directed, solutions are stable for 24 hours when stored at room temperature of 25°C and stable for 48 hours under refrigeration (2-8ºC).

PHARMACEUTICAL PRECAUTIONS
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.

CONTRAINDICATIONS
Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.
History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The selection of piperacillin / tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.
Before initiating therapy with Tazocin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.
Tazocin may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. If patients develop a skin rash they should be monitored closely and Tazocin discontinued if lesions progress.
Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Tazocin, should be discontinued.

Therapy with Tazocin may result in the emergence of resistant organisms, which might cause super-infections.
Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.
Leukopenia and neutropenia may occur, especially during prolonged therapy; therefore, periodic assessment of haematopoietic function should be performed.
As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.
Each vial of Tazocin 2 g / 0.25 g contains 5.67 mmol (130 mg) of sodium and Tazocin 4 g / 0.5 g contains 11.35 mmol (261 mg) of sodium. This should be taken into consideration for patients who are on a controlled sodium diet.
Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.
Renal Impairment
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.
In a secondary analysis using data from a large multicenter, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

DRUG-INTERACTION

Non-depolarising muscle relaxants

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanisms 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.

Oral anticoagulants

During simultaneous administration of heparin, oral anticoagulants and other substances that may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Methotrexate

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

Probenecid

As with other penicillins, concurrent administration of probenecid and piperacillin / tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

Aminoglycosides

Piperacillin, either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal

impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.
The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

Vancomycin

No pharmacokinetic interactions have been noted 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.

Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Tazocin therapy.
A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dip sticks is not affected.
The direct Coombs test may be positive.
Bio-Rad Laboratories *Platelia Aspergillus* EIA tests may lead to false-positive results for patients receiving Tazocin. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported.
Positive test results for the assays listed above in patients receiving Tazocin should be confirmed by other diagnostic methods.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no or a limited amount of data from the use of Tazocin in pregnant women.
Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic.
Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam.

Effects on ability to drive and use machines

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

UNDESIRABLE EFFECTS

The most commonly reported adverse reaction is diarrhoea (occurring in 1 patient out of 10).
Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 *		pseudo-membranous 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			hypokalaemia		
Psychiatric disorders		insomnia			
Nervous system disorders		headache			
Vascular disorders			hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, constipation, nausea, dyspepsia		stomatitis	
Hepatobiliary disorders					hepatitis*, jaundice

Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculopapular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous, purpura
Musculoskeletal and connective tissue 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.

OVERDOSE

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 dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

In the event of an overdose, piperacillin / tazobactam treatment should be discontinued. No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05

Mechanism of action

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / Pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.

Mechanism of resistance

The two main mechanisms of resistance to piperacillin / tazobactam are:

• Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.

• Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.

Additionally, alterations in bacterial membrane permeability, as well as expression of multi-drug efflux pumps, may cause or contribute to bacterial resistance to piperacillin / tazobactam, especially in Gram-negative bacteria.

Breakpoints

EUCAST Clinical MIC Breakpoints for Piperacillin / Tazobactam (2009-12-02, v 1). For Susceptibility Testing Purposes, the Concentration of Tazobactam is Fixed at 4 mg/l	
Pathogen	**Species-related breakpoints (S≤/R>)**
Enterobacteriaceae	8/16
Pseudomonas	16/16

Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

The susceptibility of *streptococci* is inferred from the penicillin susceptibility.
The susceptibility of *staphylococci* is inferred from the oxacillin susceptibility.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to piperacillin / tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus aureus, methicillin-susceptible[£]
Staphylococcus species*, coagulase negative*, methicillin-susceptible
Streptococcus pyogenes
Group B streptococci
Aerobic Gram-negative micro-organisms
Citrobacter koseri
Haemophilus influenza
Moraxella catarrhalis
Proteus mirabilis
Anaerobic Gram-positive micro-organisms
Clostridium species
Eubacterium species
Peptostreptococcus species
Anaerobic Gram-negative micro-organisms
Bacteroides fragilis group
Fusobacterium species
Porphyromonas species
Prevotella species
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecium[$,+]
Streptococcus pneumonia
Streptococcus viridans group
Aerobic Gram-negative micro-organisms

Acinetobacter baumannii[$]
Burkholderia cepacia
Citrobacter freundii
Enterobacter species
Escherichia coli
Klebsiella pneumonia
Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Corynebacterium jeikeium
Aerobic Gram-negative micro-organisms
Legionella species
Stenotrophomonas maltophilia[+,$]
Other microorganisms
Chlamydophilia pneumonia
Mycoplasma pneumonia
[$] Species showing natural intermediate susceptibility. [+] Species for which high-resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU. [£] All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.

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 / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

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

Elimination

Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.

Piperacillin is excreted rapidly as unchanged substance, 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 substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.
Following single or multiple doses of piperacillin / tazobactam to healthy subjects, the plasma half-life of piperacillin and 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 piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to slightly reduce the clearance of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.
The half-life of piperacillin and tazobactam increases 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.
Haemodialysis 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.

Paediatric population

In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) ml/min/kg. The piperacillin clearance estimate is 80% of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

Elderly patients

The mean half-life for piperacillin and tazobactam were 32% and 55% longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

Race

No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with piperacillin / tazobactam.
A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.
Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin / tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.
Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam in the rat.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
Torbac 4.5 g injection is available as vial in a carton.

STORAGE AND HANDLING INSTRUCTIONS
Store below 25ºC. Protect from light. Keep out of reach of children.

MARKETED BY

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IN/TORBAC INJECTION 4.5g/APR-17/05/PI