TAZACT Injection (Piperacillin sodium + Tazobactam sodium)

Composition

TAZACT 1.125 g
Each vial contains:
Piperacillin Sodium USP equivalent to
Piperacillin............. 1 g
Tazobactam Sodium equivalent to
Tazobactam........... 125 mg
(Sodium content 54.01 mg)

TAZACT 2.25 g
Each vial contains:
Piperacillin Sodium USP equivalent to
Piperacillin............. 2 g
Tazobactam Sodium equivalent to
Tazobactam........... 250 mg
(Sodium content 108.036 mg)

TAZACT 4.5 g
Each vial contains:
Piperacillin Sodium USP equivalent to
Piperacillin............. 4 g
Tazobactam Sodium equivalent to
Tazobactam........... 500 mg
(Sodium content 216.06 mg)

Dosage Form/s

Powder for reconstitution and intravenous (I.V.) use only.

Pharmacology

Pharmacodynamics

TAZACT (piperacillin and tazobactam) for Injection is an injectable antibacterial combination products consisting of the semisynthetic antibacterial piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium for I.V. administration.
Piperacillin, a broad-spectrum penicillin, exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. In vitro, piperacillin is active against a variety of Gram-positive and Gram-negative aerobic and anaerobic bacteria. The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.
Tazobactam sodium has little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin-binding proteins.

It is, however, a beta-lactam inhibitor of the Richmond-Sykes class III (Bush class 2b and 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a and 4) penicillinases. 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. Tazobactam does not induce chromosomally mediated beta-lactamases at tazobactam concentrations achieved with the recommended dosage regimen. Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections.

**Gram-positive Bacteria**

Staphylococcus aureus (methicillin-susceptible isolates only)

**Gram-negative Bacteria**

Acinetobacter baumannii

Escherichia coli

Haemophilus influenzae (excluding beta-lactamase-negative, ampicillin-resistant isolates)

Klebsiella pneumoniae

Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

**Gram-negative Anaerobes**

Bacteroides fragilis group (B. fragilis, B. ovatus, B. thetaiotaomicron, and B.vulgatus)

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

At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam.

However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

**Gram-positive Bacteria**

Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)

Staphylococcus epidermidis (methicillin susceptible isolates only)

*Streptococcus agalactiae*†

*Streptococcus pneumoniae*† (penicillin-susceptible isolates only)

*Streptococcus pyogenes*†

Viridans group streptococci†

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

**Gram-negative Bacteria**

Citrobacter koseri

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Providencia stuartii

Providencia rettgeri

Salmonella enterica

Gram-positive Anaerobes
Clostridium perfringens
Gram-negative Anaerobes
Bacteroides distasonis
Prevotella melaninogenica
Inherently Resistant Organisms
Gram-positive bacteria:
Corynebacterium jeikeium
Gram-negative bacteria
Legionella species
Stenotrophomonas maltophilia\(^*\)
Other bacteria
Chlamydia 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 European Union (EU).

Pharmacokinetics

Absorption
The mean and coefficients of variation (CV%) for the pharmacokinetic parameters of piperacillin and tazobactam after multiple I.V. doses are summarized in Table 1 given below.

Table 1: Mean (CV%) Piperacillin and Tazobactam Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Piperacillin/ Tazobactam Dose(^a)</th>
<th>(C_{\text{max}}) mcg/mL</th>
<th>AUC(^b) mcg·h/mL</th>
<th>CL mL/min</th>
<th>(V)</th>
<th>(T_{1/2})</th>
<th>CL(_R) mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.25 g</td>
<td>134</td>
<td>131 (14)</td>
<td>257</td>
<td>17.4</td>
<td>0.79</td>
<td>--</td>
</tr>
<tr>
<td>3.375 g</td>
<td>242</td>
<td>242 (10)</td>
<td>207</td>
<td>15.1</td>
<td>0.84</td>
<td>140</td>
</tr>
<tr>
<td>4.5 g</td>
<td>298</td>
<td>322 (16)</td>
<td>210</td>
<td>15.4</td>
<td>0.84</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Piperacillin/ Tazobactam Dose(^a)</th>
<th>(C_{\text{max}}) mcg/mL</th>
<th>AUC(^b) mcg·h/mL</th>
<th>CL mL/min</th>
<th>(V)</th>
<th>(T_{1/2})</th>
<th>CL(_R) mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.25 g</td>
<td>15</td>
<td>16.0 (21)</td>
<td>258</td>
<td>17.0</td>
<td>0.77</td>
<td>--</td>
</tr>
<tr>
<td>3.375 g</td>
<td>24</td>
<td>25.0 (8)</td>
<td>251</td>
<td>14.8</td>
<td>0.68</td>
<td>166</td>
</tr>
<tr>
<td>4.5 g</td>
<td>34</td>
<td>39.8 (15)</td>
<td>206</td>
<td>14.7</td>
<td>0.82</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^a\) Piperacillin and tazobactam were given in combination, infusied over 30 minutes.
\(^b\) Numbers in parentheses are coefficients of variation (CV\%).

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an
I.V. 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. Steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose due to the short half-lives of piperacillin and tazobactam.

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, lungs, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50% to 100% of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins (see Table 2).

Table 2: Piperacillin/Tazobactam Concentrations in Selected Tissues and Fluids after Single 4 g/0.5 g 30-minute I.V. Infusion of Piperacillin/Tazobactam

<table>
<thead>
<tr>
<th>Tissue or Fluid</th>
<th>N</th>
<th>Sampling period (h)</th>
<th>Mean PIP Concentration Range (mg/L)</th>
<th>Tissue:Plasma Range</th>
<th>Tazo Concentration Range (mg/L)</th>
<th>Tazo Tissue:Plasma Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>35</td>
<td>0.5 – 4.5</td>
<td>34.8 – 94.2</td>
<td>0.60 – 1.1</td>
<td>4.0 – 7.7</td>
<td>0.49 – 0.93</td>
</tr>
<tr>
<td>Fatty Tissue</td>
<td>37</td>
<td>0.5 – 4.5</td>
<td>4.0 – 10.1</td>
<td>0.097 – 0.115</td>
<td>0.7 – 1.5</td>
<td>0.10 – 0.13</td>
</tr>
<tr>
<td>Muscle</td>
<td>36</td>
<td>0.5 – 4.5</td>
<td>9.4 – 23.3</td>
<td>0.29 – 0.18</td>
<td>1.4 – 2.7</td>
<td>0.18 – 0.30</td>
</tr>
<tr>
<td>Proximal Intestinal Mucosa</td>
<td>7</td>
<td>1.5 – 2.5</td>
<td>31.4</td>
<td>0.55</td>
<td>10.3</td>
<td>1.15</td>
</tr>
<tr>
<td>Distal Intestinal Mucosa</td>
<td>7</td>
<td>1.5 – 2.5</td>
<td>31.2</td>
<td>0.59</td>
<td>14.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Appendix</td>
<td>22</td>
<td>0.5 – 2.5</td>
<td>26.5 – 64.1</td>
<td>0.43 – 0.53</td>
<td>9.1 – 18.6</td>
<td>0.80 – 1.35</td>
</tr>
</tbody>
</table>

*a* Each subject provided a single sample.  
*b* Time from the start of the infusion

Metabolism

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities.

Excretion

Following 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.

Both piperacillin and tazobactam are eliminated via the kidneys by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

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

Specific Populations

Renal Impairment

After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 mL/min, the increase in half-life is twofold for piperacillin and fourfold for tazobactam compared with subjects with normal renal function. Dosage adjustments for piperacillin/tazobactam are recommended when creatinine clearance is <40 mL/min in patients receiving the usual recommended daily dose of piperacillin/tazobactam.

Haemodialysis removes 30% to 40% of a piperacillin/tazobactam dose with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 16% of the tazobactam dose removed as the tazobactam metabolite.

Hepatic Impairment

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

Paediatric

Piperacillin and tazobactam pharmacokinetics were studied in paediatric patients, 2 months of age and older. The clearance of both compounds is slower in the younger patients compared with older children and adults.

In a population pharmacokinetic 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 pediatric patients 2 to 9 months old. In patients younger than 2 months of age, clearance of piperacillin is slower compared with older children; however, it is not adequately characterized for dosing recommendations. The population mean (SE) for piperacillin distribution volume is 0.243 (0.011) L/kg and is independent of age.

Geriatric

The impact of age on the pharmacokinetics of piperacillin and tazobactam was evaluated in healthy male subjects, aged 18 to 35 years (n=6) and aged 65 to 80 years (n=12). Mean half-life for piperacillin and tazobactam was 32% and 55% higher, respectively, in the elderly compared to the younger subjects. This difference may be due to age-related changes in creatinine clearance.

Race

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

Indications

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

Adolescents, Adults and the Elderly

- Lower respiratory tract infections (including moderate-to-severe nosocomial pneumonia, moderate-severity community-acquired pneumonia and ventilator-associated pneumonia)
- Complicated urinary tract infections (including pyelonephritis)
Intra-abdominal infections, including peritonitis and appendicitis complicated with rupture or abscess.

Complicated and uncomplicated skin and skin structure infections (including cellulitis, cutaneous abscesses, and ischaemic/diabetic foot infections).

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Post-partum endometritis and pelvic inflammatory disease.

Polymicrobial infections.

Bacterial septicaemia. Management of neutropaenic patients with fever suspected to be due to a bacterial infection.

Paediatric

Complicated intra-abdominal infections.

Neutropaenic children with fever suspected to be due to bacterial infections.

Dosage And Administration

Dosage

The dose and frequency of piperacillin/tazobactam depends on the severity and localization of the infection and expected pathogens.

Adolescents, Adults and the Elderly

The usual dose is 4 g piperacillin/0.5 g tazobactam given every 8 hours.

Initial presumptive treatment of patients with nosocomial pneumonia and febrile neutropenia should start with TAZACT at a dosage of 4.5 g every 6 hours plus an aminoglycoside, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients with nosocomial pneumonia in whom *Pseudomonas aeruginosa* is isolated.

The following table summarizes the treatment frequency and the recommended dose by indication or condition:

<table>
<thead>
<tr>
<th>Treatment Frequency</th>
<th>Piperacillin/Tazobactam 4 g/0.5 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropaenic adults with fever suspected to be due to a bacterial infection.</td>
</tr>
<tr>
<td>Every 8 hours</td>
<td>Complicated urinary tract infections (including pyelonephritis)</td>
</tr>
<tr>
<td></td>
<td>Complicated intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td>Skin and soft tissue infections (including diabetic foot infections)</td>
</tr>
</tbody>
</table>

The recommended dose of 4 g piperacillin/0.5 g tazobactam administered every 6 hours may also be applicable to treat patients with other indicated infections when particularly severe.

Paediatric

TAZACT can be administered in paediatric patients above 2 months of age.

Intra-abdominal Infections

- 2 months to 9 months of age: 80 mg piperacillin/10 mg tazobactam per kg q8 hours.
- 9 months or older weighing up to 40 kg: 100 mg piperacillin/12.5 mg tazobactam per kg q8 hours.
- Weighing over 40 kg: As per the adult dose.

Neutropaenia (2 to 12 years of age)
80 mg piperacillin/10 mg tazobactam per kg q6 hours.

*Dose not to exceed the maximum 4 g/0.5 g per dose over 30 minutes.*

Renal Impairment

In patients with renal impairment (creatinine clearance ≤40 mL/min) and dialysis patients (haemodialysis and CAPD), the I.V. dose of TAZACT should be reduced to the degree of actual renal function impairment. The recommended daily doses of TAZACT for patients with renal impairment are as follows:

**Adults**

The I.V. dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>TAZACT (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20 to 40</td>
<td>Maximum dose suggested: 4 g/0.5 g every 8 hours</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Maximum dose suggested: 4 g/0.5 g every 12 hours</td>
</tr>
</tbody>
</table>

For patients on haemodialysis, one additional dose of piperacillin/tazobactam 2 g/0.25 g should be administered following each dialysis period, because haemodialysis removes 30% to 50% of piperacillin in 4 hours.

**Paediatric**

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly).

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Recommended Piperacillin/Tazobactam Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>≤50</td>
<td>70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours</td>
</tr>
</tbody>
</table>

For children on haemodialysis, one additional dose of 40 mg piperacillin/5 mg tazobactam/kg should be administered following each dialysis period.

**Duration of Therapy**

The usual duration of TAZACT treatment is 5 to 14 days. However, the recommended duration of TAZACT 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.

**Method of Preparation and Administration**

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

1.125 g, 2.25 g and 4.5 g should be reconstituted with 5 mL, 10 mL and 20 mL, respectively. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes.

Use immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C), or after 48 hours if stored at refrigerated temperature (2°C to 8°C).

**Compatible Reconstitution Diluents**
I.V. injection should be given over at least 3 to 5 minutes. Reconstituted TAZACT solution should be further diluted (recommended volume per dose of 50 mL to 150 mL) with a compatible I.V. diluent solution listed below. Administer by infusion over a period of at least 20 to 30 minutes. During the infusion, it is desirable to discontinue the primary infusion solution.

**Compatible I.V. Diluent Solutions**
- 0.9% Sodium Chloride for Injection
- Sterile Water for Injection
- Dextrose 5%
- Dextran 6% in Saline
- Lactated Ringer's solution

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

Lactated Ringer's solution is not compatible with TAZACT.

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, TAZACT and the aminoglycoside are recommended for separate administration.

TAZACT and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated.

TAZACT is not compatible with tobramycin for simultaneous coadministration via Y-site infusion.

Compatibility of piperacillin and tazobactam with other aminoglycosides has not been established.

TAZACT should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. The product is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH. It should not be added to blood products or albumin hydrolysates.

TAZACT can be used in ambulatory I.V. infusion pumps.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

### Contraindications

TAZACT is contraindicated in patients with a history of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem) and history of allergic reactions to beta-lactamase inhibitors.

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.

### Warnings And Precautions

#### General

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 piperacillin/tazobactam, 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) 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.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving piperacillin/tazobactam. If patients develop a skin rash, they should be monitored closely and piperacillin/tazobactam 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, piperacillin/tazobactam should be discontinued.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including piperacillin/tazobactam, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Therapy with piperacillin/tazobactam may result in the emergence of resistant organisms, which might cause superinfections.

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.

Leukopaenia and neutropaenia associated with piperacillin/tazobactam administration appears to be reversible and may occur, especially during prolonged therapy, i.e. 21 days; therefore, periodic assessment of haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of neuromuscular excitability or convulsions may occur when high doses are administered, especially in patients with impaired renal function.

TAZACT is a monosodium salt of piperacillin and a monosodium salt of tazobactam in the combination product. This should be considered when treating patients requiring restricted salt intake. Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products or cytotoxic therapy or diuretics that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

**Drug Interactions**

**Non-Depolarizing 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-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. Monitor for adverse reactions related to neuromuscular blockade (see package
insert for vecuronium bromide).

### 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. The impact of tazobactam on the elimination of methotrexate has not been evaluated. 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. Probenecid should not be co-administered with piperacillin/tazobactam unless the benefit outweighs the risk.

### Aminoglycosides

Piperacillin may inactivate aminoglycosides by converting them to microbiologically inert amides.

When aminoglycosides are administered in conjunction with piperacillin to patients with end-stage renal disease requiring haemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly reduced and should be monitored.

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. No dosage adjustment is considered necessary.

The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

Due to in vitro inactivation, of aminoglycoside by piperacillin, piperacillin/tazobactam and aminoglycosides are recommended for separate administration.

Piperacillin/tazobactam is not compatible with tobramycin for simultaneous Y-site infusion.

### 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. Monitor kidney function in patients concomitantly administered with piperacillin/tazobactam and vancomycin.

### Effects on Laboratory Tests

Non-enzymatic methods of measuring urinary glucose (like the copper-reduction method) may lead to false-positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under piperacillin/tazobactam therapy.

A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dipsticks is not affected.

The direct Coombs test may be positive.
BioRad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving piperacillin/tazobactam. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with BioRad Laboratories Platelia Aspergillus EIA test have been reported. Positive test results for the assays listed above in patients receiving piperacillin/tazobactam should be confirmed by other diagnostic methods.

**Renal Impairment**

In patients with creatinine clearance ≤40 mL/min and dialysis patients (haemodialysis and CAPD), the I.V. dose of piperacillin/tazobactam should be reduced to the degree of renal function impairment. Please refer to DOSAGE AND ADMINISTRATION.

**Hepatic Impairment**

No dosage adjustment of piperacillin/tazobactam is necessary in patients with hepatic impairment (including cirrhosis). The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared with healthy subjects.

**Pregnancy**

*Pregnancy Category B*

There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Both 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.

**Lactation**

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when piperacillin/tazobactam is administered to a nursing mother.

**Paediatric Use**

Safety and efficacy in paediatric patients less than 2 months of age have not been established. For data on renal impairment, please refer to DOSAGE AND ADMINISTRATION. No data are available in case of paediatric patients with impaired hepatic function.

**Geriatric Use**

Patients over 65 years of age are not an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal impairment. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. TAZACT is a monosodium salt of piperacillin and a monosodium salt of tazobactam in the combination product. This should be considered when treating the elderly patients requiring restricted salt intake. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

**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 pseudomembranous 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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Frequency not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>thrombocytopenia, anaemia*, Coombs direct test positive, activated partial thromboplastin time prolonged</td>
<td>leukopenia, prothrombin time prolonged</td>
<td>agranulocytosis, epistaxis</td>
<td>pancytopenia*, neutropenia, haemolytic anaemia*, purpura, bleeding time prolonged, thrombocytosis*, eosinophilia*</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>blood albumin decreased, protein total decreased</td>
<td>hypokalaemia, blood glucose decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, insomnia</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td>hypotension, phlebitis, thrombophlebitis, flushing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea</td>
<td>abdominal pain, vomiting, nausea, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, stomatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased</td>
<td>blood bilirubin increased</td>
<td></td>
<td>hepatitis*, jaundice, gamma-glutamyl transferase increased</td>
<td></td>
</tr>
</tbody>
</table>
Skin and subcutaneous tissue disorders

- rash, pruritus
- erythema multiforme*, urticaria, rash maculopapular*
- toxic epidermal necrolysis*
- Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous

Musculoskeletal and connective tissue disorders

- arthralgia, myalgia

Renal and urinary disorders

- blood creatinine increased, blood urea increased
- renal failure, tubulointerstitial nephritis*

General disorders and administration site conditions

- pyrexia, injection site reaction
- Chills

*Adverse drug reactions identified post-marketing

Other general adverse events include fever and rigor while adverse laboratory events (seen during clinical trials) include decrease in haemoglobin and haematocrit, increases in platelet count, abnormalities in electrolytes (i.e. increases and decreases in sodium, potassium, and calcium), and hyperglycaemia. Eosinophilic pneumonia and dermatitis exfoliative have also been identified during post-approval use of piperacillin/tazobactam. Additionally, prolonged muscle relaxation has also been reported for piperacillin for injection. Piperacillin/tazobactam was also found to be associated with increased incidence of bronchospasm.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis. Clinical trials and postmarketing experiences of piperacillin/tazobactam in paediatric patients suggest a similar safety profile to that seen in adults.

**Overdosage**

**Symptoms**

There have been postmarketing 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 I.V. doses are given (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.

**Incompatibility**

TAZACT should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been
TAZACT is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH. Lactated Ringer's solution is not compatible with TAZACT. TAZACT should not be added to blood products or albumin hydrolysates. When concomitant therapy with aminoglycosides is indicated, TAZACT and the aminoglycoside should be reconstituted and administered separately, due to the in vitro inactivation of the aminoglycoside by the penicillin. TAZACT is not compatible with tobramycin for simultaneous co-administration via Y-site infusion. Compatibility of piperacillin and tazobactam with other aminoglycosides has not been established.

**Storage And Handling Instructions**

### Before Opening

Store at controlled room temperature between 15° and 30°C.

### Reconstituted Solutions

Discard any unused portion after 24 hours if stored at room temperature or after 48 hours if refrigerated (2° to 8°C). Vials should not be frozen after reconstitution.

**Packaging Information**

- TAZACT 1.125 g: Vial of 10 mL
- TAZACT 2.25 g: Vial of 20 mL
- TAZACT 4.5 g: Vial of 30 mL

Last Reviewed: November 2017

Last Updated: November 2017

**TAZACT Injection**

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