Public Assessment Report

Decentralised Procedure

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion

Procedure Nos: UK/H/1010-2/001-2/DC

UK Licence Nos: PL 14894/0487-92

Ranbaxy (UK) Limited
LAY SUMMARY

On 21 March 2010, Belgium, the Czech Republic, Denmark, Finland, Hungary, the Netherlands, Poland, Portugal, the Slovak Republic, Sweden and the UK agreed to grant Marketing Authorisations to Ranbaxy (UK) Limited for the medicinal products Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion (PL 14894/0487-92; UK/H/1010-2/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 24 November 2010.

These are prescription-only medicines (POM) used to treat adults, including the elderly, with bacterial infections, such as those affecting your chest, urinary tract, blood, abdomen or skin. Piperacillin/Tazobactam may also be used to treat infections in adults and children aged 2 to 12, who are unable to fight infections normally due to low white cell counts.

These products contain the active ingredients piperacillin sodium and tazobactam sodium. Piperacillin sodium belongs to the group of medicines known as ‘broad spectrum antibiotics’. Antibiotics are used to kill the bacteria (‘germs’) which cause infection. Piperacillin sodium can kill many kinds of bacteria. Tazobactam sodium can prevent some bacteria becoming resistant to the effects of piperacillin sodium. This means that some bacteria, which are not normally killed by piperacillin sodium, are killed when piperacillin sodium and tazobactam sodium are given together.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion outweigh the risks; hence Marketing Authorisations were granted.
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# Module 1

## Information about the initial procedure

| Product Names | Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion  
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
</tbody>
</table>
| Active Substances | Piperacillin sodium  
Tazobactam sodium |
| Form | Powder for Solution for Injection or Infusion |
| Strength | 2 g/0.25 g and 4 g/0.5 g piperacillin/tazobactam |
| MA Holder | Ranbaxy (UK) Limited  
Building 4, Chiswick Park,  
566 Chiswick High Road, London, W4 5YE  
United Kingdom |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | UK/H/1010/001-2/DC: Portugal  
UK/H/1011/001-2/DC: Denmark, Finland, Sweden  
UK/H/1012/001-2/DC: Belgium, Czech Republic, Hungary, the Netherlands, Poland, the Slovak Republic |
| Procedure Number | UK/H/1010-2/001-2/DC |
| Timetable | Day 210 – 21 March 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin sodium equivalent to 2 g piperacillin and tazobactam sodium equivalent to 0.25 g tazobactam.

‘Each vial contains 105 mg of sodium.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion.

White or off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Piperacillin/tazobactam is indicated for treatment of moderate to severe systemic and/or local bacterial infections in which beta-lactamase producing bacteria (see section 5.1) are suspected or have been detected, such as:

Adults/Adolescents and the Elderly
Nosocomial pneumonia
Complicated urinary tract infections (including pyelonephritis)
Intra-abdominal infections
Skin and soft tissue infections
Bacterial infections in neutropenic adults

Children (2-12 years)
Bacterial infections in neutropenic children

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Piperacillin/tazobactam may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes).

For reconstitution instructions, see section 6.6.

The treatment of mixed infections caused by piperacillin susceptible organisms and beta-lactamase producing organisms susceptible to piperacillin/tazobactam generally do not require the addition of another antibiotic.

In patients with nosocomial pneumonia and infections in neutropenic patients piperacillin/tazobactam can be used with an aminoglycoside. If the use of an aminoglycoside is needed with piperacillin/tazobactam, both piperacillin/tazobactam and the aminoglycoside must be used in completely therapeutic doses.

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, Each with Normal Renal Function
The usual dosage for adults and children over 12 years is piperacillin/tazobactam 4000/500 mg given every 8 hours.
The total daily dose of piperacillin/tazobactam depends on the severity and localisation of the infection and can vary from piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg administered every 6 or 8 hours.

In neutropenia the recommended dose is piperacillin/tazobactam 4000/500 mg given every 6 hours in combination with an aminoglycoside.

**Elderly with Normal Renal Function**

Piperacillin/tazobactam may be used at the same dose levels as adults except in cases of renal impairment (see below):

**Renal Insufficiency in Adults, the Elderly and Children (over 40 kg) Receiving the Adult Dose**

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended Piperacillin/Tazobactam dosage</th>
<th>Frequency</th>
<th>Maximum daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 80</td>
<td>12/1.5 g /day</td>
<td>4000/500 mg q 8H</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>8/1 g /day</td>
<td>4000/500 mg q 12H</td>
<td></td>
</tr>
</tbody>
</table>

For patients on haemodialysis, the maximum daily dose is piperacillin/tazobactam 8/1 g. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of piperacillin/tazobactam 2000/250 mg should be administered following each dialysis period.

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

**Children Aged 2-12 Years with Normal Renal Function**

Piperacillin/tazobactam is only recommended for the treatment of children with neutropenia.

**Neutropenia**

For children weighing less than 40 kg the dose should be adjusted to 90mg/kg (piperacillin/tazobactam 80/10 mg) administered every 6 hours, in combination with an aminoglycoside, not exceeding piperacillin/tazobactam 4000/500 mg every 6 hours.

**Renal Insufficiency in Children Aged 2-12 Years (or bodyweight less than 40 kg)**

In children with renal insufficiency the intravenous dosage should be adjusted to the degree of actual renal impairment as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended piperacillin/tazobactam dosage</th>
<th>Frequency</th>
<th>Maximum daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>No adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>90 mg (piperacillin/tazobactam 80/10 mg)</td>
<td>q 8H</td>
<td>12/1.5 g /day</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>90 mg (piperacillin/tazobactam 80/10 mg)</td>
<td>q 12H</td>
<td>8/1 g /day</td>
</tr>
</tbody>
</table>

For children weighing < 50 kg on haemodialysis the recommended dose is 45 mg (piperacillin/tazobactam 40/5 mg) /kg every 8 hours.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

**Children under 2 years**

Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

**Hepatic Impairment**

No dose adjustment is necessary.

**Duration of Therapy**

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.
4.3 Contraindications
Hypersensitivity to penicillin or any of the beta-lactam antibiotics and to tazobactam or any other beta-lactamase inhibitors.

4.4 Special warnings and precautions for use

Warnings
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.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe reactions when treated with a cephalosporin.

If an allergic reaction occurs during therapy with piperacillin/tazobactam, the antibiotic should be discontinued. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Before initiating therapy with piperacillin/tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced, life threatening pseudomembranous colitis must be taken into consideration. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Therefore, piperacillin/tazobactam must be discontinued immediately in such cases, and suitable therapy should be initiated.

Precautions
Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of a full blood count should be performed.

Periodic assessment of organ system functions including renal and hepatic during prolonged therapy is advisable.

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

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfection. If this occurs, appropriate measures should be taken.

Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

This medicinal product contains 4.72 mmol (109 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into account by patients on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations should be performed in such patients. Modest elevation of indices of liver function may be observed.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients (see also 4.8).

Until further experience is available, piperacillin/tazobactam should not be used in children who do not have neutropenia or complicated appendicitis.
4.5 Interaction with other medicinal products and other forms of interaction

Interaction with probenacid:
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 either drug are unaffected.

Interaction with antibiotics:
No clinically relevant adverse pharmacokinetic interaction with tobramycin or vancomycin has been observed in healthy adults with a normal renal function. The clearance of tobramycin and gentamicin was enhanced in patients with severe renal dysfunction using piperacillin/tazobactam. In these patients mixing of piperacillin/tazobactam formulation with tobramycin and gentamicin was excluded.

For information related to the administration of piperacillin/tazobactam with aminoglycosides please refer to section 6.2.

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

Interaction with vecuronium:
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. This should be taken into account when piperacillin/tazobactam is used peri-operatively.

Interaction with methotrexate:
Piperacillin may reduce the excretion of methotrexate. Serum levels of methotrexate should be monitored in patients on methotrexate therapy.

Interaction with laboratory test results:
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 reaction be used.

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

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies with piperacillin/tazobactam in combination or with piperacillin or tazobactam alone in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). Piperacillin and tazobactam cross the placenta. Piperacillin/tazobactam should only be used during pregnancy if clearly indicated.

Piperacillin is excreted in low concentrations in human milk. Tazobactam concentrations in human milk have not been studied. The effect on the sucking infant is unknown. Women who are breast-feeding should be treated only if clearly indicated. Diarrhoea and fungal infections of the mucous membranes as well as sensitisation could occur in the breast-fed infant.

4.7 Effects on ability to drive and use machines

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

However, side effects may occur (see also 4.8), which may influence the ability to drive and use machines.
4.8 Undesirable effects

Undesirable effects are listed by frequency as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10000); not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are diarrhoea, nausea, vomiting, and rash, each having a frequency of ≥ 1% but ≤ 10%.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Candidal superinfection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Agranulocytosis, Coombs’ direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaphylactic/anaphylactoid reaction (including shock)</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>Very rare</td>
<td>Hypoalbuminaemia, hypoglycaemia, hypoproteininaemia, hypokalaemia.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache, insomnia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Muscular weakness, hallucination, convulsion</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension, phlebitis, thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Flushing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Constipation, dyspepsia, jaundice, stomatitis</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Abdominal pain, pseudomembranous colitis, dry mouth</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Alanine aminotransferase increased, aspartate aminotransferase increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bilirubin increased, blood alkaline phosphatase increased, gamma- glutamyltransferase increased, hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash including maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Pruritus, urticaria, erythema</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Stevens-Johnson Syndrome, toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Rare</td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Interstitial nephritis, renal failure</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Blood urea nitrogen increased</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Fever, injection site reaction</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Rigors, tiredness, oedema</td>
</tr>
</tbody>
</table>

The administration of high doses of beta-lactams, particularly in patients with renal insufficiency, can lead to encephalopathies (consciousness fluctuation, myoclonus and convulsions).

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.
4.9 **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 dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

**Treatment of Intoxication**
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. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (for more details see section 5.2).

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

**Pharmacotherapeutic group:** Combinations of penicillins, including beta-lactamase inhibitors

**ATC Classification:** J01CR05

**Mechanism of action**
Piperacillin, a broad spectrum, semi-synthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

**Pharmacokinetic/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 presence of tazobactam expands the spectrum of activity of piperacillin to include microorganisms that would otherwise, due to the formation of beta-lactamase, be resistant to piperacillin and other beta-lactam antibiotics. *In vitro* investigation has demonstrated that the type I beta-lactamase inducing ability of tazobactam is insignificant with regard to Gram-negative bacteria. *In vitro* studies have demonstrated a synergetic effect of piperacillin/tazobactam and aminoglycosides against *Pseudomonas aeruginosa* and other bacteria, including beta-lactamase producing strains.
Breakpoints

The EUCAST break points are given as below:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC breakpoints (mg/L)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤</td>
<td>≥</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>1E</td>
<td>1E</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp</td>
<td>Note 1,2,3</td>
<td>Note 1,2,3</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp</td>
<td>Note 1</td>
<td>Note 1</td>
</tr>
<tr>
<td><em>Streptococcus</em> groups A, B, C and G</td>
<td>Note 1</td>
<td>Note 1</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Note 1,2</td>
<td>Note 1,2</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>Note 1</td>
<td>Note 1</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Note 1</td>
<td>Note 1</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>IP</td>
<td>IP</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gram-positive anaerobes</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Gram-negative anaerobes</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

IE= indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

IP= In Preparation

Notes:

1/ Isolates without beta-lactamase and oxacillin/cefoxitin-susceptible are susceptible to all penicillins for which breakpoints are given. The benzylpenicillin breakpoint will mostly, but not unequivocally, separate beta-lactamase producers from non-producers. Most staphylococci are penicillinase-producers. Penicillinase-producing strains are resistant to benzylpenicillin, phenoxymethylpenicillin, amino-, carboxy- and ureidopenicillins.

2/ Isolates with methicillin resistance (oxacillin/cefoxitin resistant) are resistant to all currently available β-lactam agents, including β-lactamase inhibitor combinations.

3/ Isolates with beta-lactamase production but without methicillin (oxacillin/cefoxitin) resistance are susceptible to penicillin-beta-lactamase inhibitor combinations and penicillinase-resistant penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin).

4/ Susceptibility to ampicillin and amoxicillin and piperacillin with and without beta lactamase inhibitor can be inferred from the ampicillin susceptibility test.

5/ The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

6/ Most MIC values for penicillin, ampicillin, amoxicillin and piperacillin (with or without a beta-lactamase inhibitor) differ by no more than one dilution step and isolates fully susceptible to benzylpenicillin (MIC≤0.064 mg/L; susceptible by oxacillin disk screen, can be reported susceptible to beta-lactam agents that have been given breakpoints.

7/ Isolates fully susceptible to benzylpenicillin (MIC≤0.064 mg/L; susceptible by oxacillin disk screen, can be reported susceptible to ampicillin, amoxicillin and piperacillin (with or without beta-lactamase inhibitor) without further testing. Otherwise use ampicillin to categorize susceptibility to ampicillin, amoxicillin and piperacillin.

8/ In endocarditis, refer to national or international endocarditis guidelines for breakpoints for viridans streptococci.

9/ Isolates susceptible to ampicillin and amoxicillin are also susceptible to piperacillin and piperacillin-tazobactam and isolates susceptible to amoxicillin-clavulanate are also susceptible to piperacillin-tazobactam.

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.
Commonly susceptible species
Gram positive aerobes
Brevibacterium spp
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus spp. methicillin-sensitive
Streptococcus pneumoniae
Streptococcus pyogenes
Group B streptococci
Streptococcus spp*

Gram negative aerobes
Branhamella catarrhalis
Citrobacter koseri
Haemophilus influenzae*
Haemophilus spp.
Proteus mirabilis
Salmonella spp.
Shigella spp.
Gram positive anaerobes
Clostridium spp.
Eubacterium spp.
Peptococcus spp.
Peptostreptococcus spp.

Gram negative anaerobes
Bacteroides fragilis*
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp*

Species for which resistance may be a problem
Gram positive aerobes
Staphylococcus aureus, methicillin-sensitive
Staphylococcus epidermis, methicillin-sensitive
Enterococcus avium ($)
Enterococcus faecium (+ $)
Propionibacterium acnes ($)
Viridans streptococci

Gram negative aerobes
Actinobacter spp (+ $)
Burkholderia cepacia
Citrobacter freundii
Enterobacter spp.
Escherichia coli *
Klebsiella spp.
Proteus, indole positive
Pseudomonas aeruginosa*
Pseudomonas spp. *
Pseudomonas stutzeri $
Serratia spp.

Gram negative anaerobes
Bacteroides spp.*
Inherently resistant organisms
Gram positive aerobes
Corynebacterium jeikeium
Staphylococcus spp. methicillin resistant

Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilia +$
* Clinical effectiveness against this has been demonstrated in the registered indications.
($) 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.

5.2 Pharmacokinetic properties

Distribution
Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion or injection. Piperacillin plasma levels produced when given with tazobactam are similar to those attained when equivalent doses of piperacillin are administered alone.

There is a greater proportional (approximately 28%) increase in plasma levels of piperacillin and tazobactam with increasing dose over the dosage range of piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg.

Both piperacillin and tazobactam are 20 to 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 tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.

Biotransformation
Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite which has been found to be micro-biologically inactive.

Elimination
Piperacillin and tazobactam are eliminated by the kidney via 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 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 reduce the rate of elimination of tazobactam.

Impaired Renal Function
Piperacillin and tazobactam are haemodialysable: 31% (piperacillin) and 39% (tazobactam) of administered doses are filtrated. During peritoneal dialysis, 5% of administered piperacillin and 12% of administered tazobactam are found in the dialysis liquid. Patients treated by chronic ambulatory peritoneal dialysis should receive the same dose as non dialysed patients with severe renal insufficiency.

Impaired Liver Function
Plasma concentrations of piperacillin and tazobactam are prolonged in hepatically impaired patients. The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustments in patients with hepatic impairment are not necessary.
**Paediatric patients**

The pharmacokinetics of piperacillin/tazobactam has been studied in paediatric patients with intra-abdominal infections and other kinds of infections. In every age group, renal fraction of elimination of piperacillin and tazobactam was approximately 70% and 80%, respectively, like in adults.

Mean pharmacokinetic parameters of piperacillin/tazobactam of paediatric patients of different age groups.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Piperacillin Half-life (hr)</th>
<th>Piperacillin Clearance (ml/min/kg)</th>
<th>Tazobactam Half-life (hr)</th>
<th>Tazobactam Clearance (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 years</td>
<td>0.7</td>
<td>5.5</td>
<td>0.8</td>
<td>5.5</td>
</tr>
<tr>
<td>6-12 years</td>
<td>0.7</td>
<td>5.9</td>
<td>0.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

5.3 **Preclinical safety data**

Preclinical 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 study of piperacillin/tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs following i.p. administration to rats. Fertility of the F1 generation and embryonic development of the F2 generation was not impaired. A teratogenicity study in rats, did not show teratogenic effects after i.v. administration. In the rat, effects on the embryonic development were observed at maternal toxic doses. Peri/postnatal development was impaired (reduced fetal weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after i.p. administration in the rat.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

None.

6.2 **Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

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

Piperacillin/tazobactam should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's solution is not compatible with piperacillin/tazobactam.

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

6.3 **Shelf life**

2 years

**After reconstitution:**

Chemical and physical in-use stability has been demonstrated for **24 hours when stored in a refrigerator at 2-8°C**.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.
6.4 **Special precautions for storage**

Store below 25°C.

For storage or reconstituted solution, please refer to section 6.3.

6.5 **Nature and contents of container**

Each cardboard carton contains 1 vial of Type II 20 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial ; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

**Reconstitution Directions**

**Intravenous Injection**

Each vial of piperacillin/tazobactam 2.25 g (piperacillin 2000 mg/tazobactam 250 mg) should be reconstituted with 10 ml of one of the following diluents.

- Sterile Water for Injection
- 0.9% Sodium Chloride for Injection

Swirl until dissolved.

**Intravenous Infusion**

Each vial of piperacillin/tazobactam 2.25 g (piperacillin 2000 mg/tazobactam 250 mg) should be reconstituted with 10 ml of one of the above diluents. The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with Dextrose 5% in Water.

**Displacement Volume**

Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml.

2.25 g piperacillin/tazobactam (piperacillin 2000 mg/tazobactam 250 mg) will displace 1.58 ml

For single use only. Discard any unused solution.

The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0487, PL 14894/0489, PL 14894/0491

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

24/11/2010

10 **DATE OF REVISION OF THE TEXT**

24/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin sodium equivalent to 4 g piperacillin and tazobactam sodium equivalent to 0.5 g tazobactam.

‘Each vial contains 210 mg of sodium.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion.

White or off white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Piperacillin/tazobactam is indicated for treatment of moderate to severe systemic and/or local bacterial infections in which beta-lactamase producing bacteria (see section 5.1) are suspected or have been detected, such as:

*Adults/Adolescents and the Elderly*
Nosocomial pneumonia
Complicated urinary tract infections (including pyelonephritis)
Intra-abdominal infections
Skin and soft tissue infections
Bacterial infections in neutropenic adults

*Children (2-12 years)*
Bacterial infections in neutropenic children

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Piperacillin/tazobactam may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes).

For reconstitution instructions, see section 6.6.

The treatment of mixed infections caused by piperacillin susceptible organisms and beta-lactamase producing organisms susceptible to piperacillin/tazobactam generally do not require the addition of another antibiotic.

In patients with nosocomial pneumonia and infections in neutropenic patients piperacillin/tazobactam can be used with an aminoglycoside. If the use of an aminoglycoside is needed with piperacillin/tazobactam, both piperacillin/tazobactam and the aminoglycoside must be used in completely therapeutic doses.

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, Each with Normal Renal Function*
The usual dosage for adults and children over 12 years is piperacillin/tazobactam 4000/500 mg given every 8 hours.

The total daily dose of piperacillin/tazobactam depends on the severity and localisation of the infection and can vary from piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg administered every 6 or 8 hours.

In neutropenia the recommended dose is piperacillin/tazobactam 4000/500 mg given every 6 hours in combination with an aminoglycoside.
**Elderly with Normal Renal Function**
Piperacillin/tazobactam may be used at the same dose levels as adults except in cases of renal impairment (see below):

**Renal Insufficiency in Adults, the Elderly and Children (over 40 kg) Receiving the Adult Dose**
In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended Piperacillin/Tazobactam dosage</th>
<th>Frequency</th>
<th>Maximum daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Divided doses</td>
<td></td>
</tr>
<tr>
<td>20 - 80</td>
<td>12/1.5 g /day</td>
<td>4000/500 mg q 8H</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>8/1 g /day</td>
<td>4000/500 mg q 12H</td>
<td></td>
</tr>
</tbody>
</table>

For patients on haemodialysis, the maximum daily dose is piperacillin/tazobactam 8/1 g. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of piperacillin/tazobactam 2000/250 mg should be administered following each dialysis period.

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

**Children Aged 2-12 Years with Normal Renal Function**
Piperacillin/tazobactam is only recommended for the treatment of children with neutropenia.

**Neutropenia**
For children weighing less than 40 kg the dose should be adjusted to 90mg/kg (piperacillin/tazobactam 80/10 mg) administered every 6 hours, in combination with an aminoglycoside, not exceeding piperacillin/tazobactam 4000/500 mg every 6 hours.

**Renal Insufficiency in Children Aged 2-12 Years (or bodyweight less than 40 kg)**
In children with renal insufficiency the intravenous dosage should be adjusted to the degree of actual renal impairment as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended piperacillin/tazobactam dosage</th>
<th>Frequency</th>
<th>Maximum daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>No adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>90 mg (piperacillin/tazobactam 80/10 mg) /kg</td>
<td>q 8H</td>
<td>12/1.5 g /day</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>90 mg (piperacillin/tazobactam 80/10 mg) /kg</td>
<td>q 12H</td>
<td>8/1 g /day</td>
</tr>
</tbody>
</table>

For children weighing < 50 kg on haemodialysis the recommended dose is 45 mg (piperacillin/tazobactam 40/5 mg) /kg every 8 hours.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

**Children under 2 years**
Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

**Hepatic Impairment**
No dose adjustment is necessary.

**Duration of Therapy**
The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

**4.3 Contraindications**
Hypersensitivity to penicillin or any of the beta-lactam antibiotics and to tazobactam or any other beta-lactamase inhibitors.
4.4 Special warnings and precautions for use

**Warnings**

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.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe reactions when treated with a cephalosporin.

If an allergic reaction occurs during therapy with piperacillin/tazobactam, the antibiotic should be discontinued. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Before initiating therapy with piperacillin/tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced, life threatening pseudomembranous colitis must be taken into consideration. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Therefore, piperacillin/tazobactam must be discontinued immediately in such cases, and suitable therapy should be initiated.

**Precautions**

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of a full blood count should be performed.

Periodic assessment of organ system functions including renal and hepatic during prolonged therapy is advisable.

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

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfection. If this occurs, appropriate measures should be taken.

Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into account by patients on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations should be performed in such patients. Modest elevation of indices of liver function may be observed.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients (see also 4.8).

Until further experience is available, piperacillin/tazobactam should not be used in children who do not have neutropenia or complicated appendicitis.

4.5 Interaction with other medicinal products and other forms of interaction

**Interaction with probenacid**:

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 either drug are unaffected.

**Interaction with antibiotics**:

No clinically relevant adverse pharmacokinetic interaction with tobramycin or vancomycin has been observed in healthy adults with a normal renal function. The clearance of tobramycin and gentamicin
was enhanced in patients with severe renal dysfunction using piperacillin/tazobactam. In these patients mixing of piperacillin/tazobactam formulation with tobramycin and gentamicin was excluded.

For information related to the administration of piperacillin/tazobactam with aminoglycosides please refer to section 6.2.

**Interaction with anticoagulants:**
During simultaneous administration of heparin, oral anticoagulants and other drugs which may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

**Interaction with vecuronium:**
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. This should be taken into account when piperacillin/tazobactam is used peri-operatively.

**Interaction with methotrexate:**
Piperacillin may reduce the excretion of methotrexate. Serum levels of methotrexate should be monitored in patients on methotrexate therapy.

**Interaction with laboratory test results:**
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 reaction be used.

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

### 4.6 Pregnancy and lactation
There are no adequate and well-controlled studies with piperacillin/tazobactam in combination or with piperacillin or tazobactam alone in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). Piperacillin and tazobactam cross the placenta. Piperacillin/tazobactam should only be used during pregnancy if clearly indicated.

Piperacillin is excreted in low concentrations in human milk. Tazobactam concentrations in human milk have not been studied. The effect on the sucking infant is unknown. Women who are breast-feeding should be treated only if clearly indicated. Diarrhoea and fungal infections of the mucous membranes as well as sensitisation could occur in the breast-fed infant.

### 4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

However, side effects may occur (see also 4.8), which may influence the ability to drive and use machines.
4.8 Undesirable effects

Undesirable effects are listed by frequency as follows: 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); very rare (≤ 1/10 000); not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are diarrhoea, nausea, vomiting, and rash, each having a frequency of ≥ 1% but ≤ 10%.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Candidal superinfection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Agranulocytosis, Coombs’ direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaphylactic/anaphylactoid reaction (including shock)</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>Very rare</td>
<td>Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache, insomnia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Muscular weakness, hallucination, convulsion</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension, phlebitis, thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Flushing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Constipation, dyspepsia, jaundice, stomatitis</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Abdominal pain, pseudomembranous colitis, dry mouth</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Alanine aminotransferase increased, aspartate aminotransferase increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bilirubin increased, blood alkaline phosphatase increased, gamma- glutamyltransferase increased, hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash including maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Pruritus, urticaria, erythema</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Stevens-Johnson Syndrome, toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Rare</td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Interstitial nephritis, renal failure</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Blood urea nitrogen increased</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Fever, injection site reaction</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Rigors, tiredness, oedema</td>
</tr>
</tbody>
</table>

The administration of high doses of beta-lactams, particularly in patients with renal insufficiency, can lead to encephalopathies (consciousness fluctuation, myoclonus and convulsions).

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.
4.9 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 dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment of Intoxication
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. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (for more details see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, including beta-lactamase inhibitors

ATC Classification: J01CR05

Mechanism of action
Piperacillin, a broad spectrum, semi-synthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacokinetic/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 presence of tazobactam expands the spectrum of activity of piperacillin to include microorganisms that would otherwise, due to the formation of beta-lactamase, be resistant to piperacillin and other beta-lactam antibiotics. In vitro investigation has demonstrated that the type I beta-lactamase inducing ability of tazobactam is insignificant with regard to Gram-negative bacteria. In vitro studies have demonstrated a synergetic effect of piperacillin/tazobactam and aminoglycosides against Pseudomonas aeruginosa and other bacteria, including beta-lactamase producing strains.
Breakpoints
The EUCAST break points are given as below:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC breakpoints (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>16</td>
</tr>
<tr>
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</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4</td>
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</tbody>
</table>

IE= indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.
IP= In Preparation

Notes:
1/ Isolates without beta-lactamase and oxacillin/cefoxitin-susceptible are susceptible to all penicillins for which breakpoints are given. The benzylpenicillin breakpoint will mostly, but not unequivocally, separate beta-lactamase producers from non-producers. Most staphylococci are penicillinase-producers. Penicillinase-producing strains are resistant to benzylpenicillin, phenoxymethylpenicillin, amino-, carboxy- and ureidopenicillins.
2/ Isolates with methicillin resistance (oxacillin/cefoxitin resistant) are resistant to all currently available β-lactam agents, including β-lactamase inhibitor combinations.
3/ Isolates with beta-lactamase production but without methicillin (oxacillin/cefoxitin) resistance are susceptible to penicillin-beta-lactamase inhibitor combinations and penicillinase-resistant penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin).
4/ Susceptibility to ampicillin and amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferred from the ampicillin susceptibility test.
5/ The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.
6/ Most MIC values for penicillin, ampicillin, amoxicillin and piperacillin (with or without a beta-lactamase inhibitor) differ by no more than one dilution step and isolates fully susceptible to benzylpenicillin (MIC≤0.064 mg/L; susceptible by oxacillin disk screen, can be reported susceptible to beta-lactam agents that have been given breakpoints.
7/ Isolates fully susceptible to benzylpenicillin (MIC≤0.064 mg/L; susceptible by oxacillin disk screen, can be reported susceptible to ampicillin, amoxicillin and piperacillin (with or without beta-lactamase inhibitor) without further testing. Otherwise use ampicillin to categorize susceptibility to ampicillin, amoxicillin and piperacillin.
8/ In endocarditis, refer to national or international endocarditis guidelines for breakpoints for viridans streptococci.
9/ Isolates susceptible to ampicillin and amoxicillin are also susceptible to piperacillin and piperacillin-tazobactam and isolates susceptible to amoxicillin-clavulanate are also susceptible to piperacillin-tazobactam.

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.
**Commonly susceptible species**

Gram positive aerobes
- Brevibacterium spp
- Enterococcus faecalis
- Listeria monocytogenes
- Staphylococcus spp. methicillin-sensitive
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Group B streptococci
- Streptococcus spp*

Gram negative aerobes
- Branhamella catarrhalis
- Citrobacter koseri
- Haemophilus influenzae*
- Haemophilus spp.
- Proteus mirabilis
- Salmonella spp.
- Shigella spp.

Gram positive anaerobes
- Clostridium spp.
- Eubacterium spp.
- Peptococcus spp.
- Peptostreptococcus spp.

Gram negative anaerobes
- Bacteroides fragilis*
- Bacteroides fragilis group
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp*

**Species for which resistance may be a problem**

Gram positive aerobes
- Staphylococcus aureus, methicillin-sensitive
- Staphylococcus epidermis, methicillin-sensitive
- Enterococcus avium ($)  
- Enterococcus faecium (+ $)
- Propionibacterium acnes (§)
- Viridans streptococci

Gram negative aerobes
- Actinobacter spp (+ $)
- Burkholderia cepacia
- Citrobacter freundii
- Enterobacter spp.
- Escherichia coli *
- Klebsiella spp.
- Proteus, indole positive
- Pseudomonas aeruginosa*
- Pseudomonas spp. *
- Pseudomonas stutzeri §
- Serratia spp.

Gram negative anaerobes
- Bacteroides spp. *
Inherently resistant organisms
Gram positive aerobes
Corynebacterium jeikeium
Staphylococcus spp. methicillin resistant

Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilia +$

* Clinical effectiveness against this has been demonstrated in the registered indications.
($) 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.

5.2 Pharmacokinetic properties

Distribution
Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion or injection. Piperacillin plasma levels produced when given with tazobactam are similar to those attained when equivalent doses of piperacillin are administered alone.

There is a greater proportional (approximately 28%) increase in plasma levels of piperacillin and tazobactam with increasing dose over the dosage range of piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg.

Both piperacillin and tazobactam are 20 to 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 tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.

Biotransformation
Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite which has been found to be micro-biologically inactive.

Elimination
Piperacillin and tazobactam are eliminated by the kidney via 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 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 reduce the rate of elimination of tazobactam.

Impaired Renal Function
Piperacillin and tazobactam are haemodialysable: 31% (piperacillin) and 39% (tazobactam) of administered doses are filtrated. During peritoneal dialysis, 5% of administered piperacillin and 12% of administered tazobactam are found in the dialysis liquid. Patients treated by chronic ambulatory peritoneal dialysis should receive the same dose as non dialysed patients with severe renal insufficiency.

Impaired Liver Function
Plasma concentrations of piperacillin and tazobactam are prolonged in hepatically impaired patients. The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustments in patients with hepatic impairment are not necessary.
**Paediatric patients**

The pharmacokinetics of piperacillin/tazobactam has been studied in paediatric patients with intra-abdominal infections and other kinds of infections. In every age group, renal fraction of elimination of piperacillin and tazobactam was approximately 70% and 80%, respectively, like in adults.

Mean pharmacokinetic parameters of piperacillin/tazobactam of paediatric patients of different age groups.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Piperacillin</th>
<th>Tazobactam</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Half-life</td>
<td>Clearance</td>
</tr>
<tr>
<td>2-5 years</td>
<td>0.7</td>
<td>5.5</td>
</tr>
<tr>
<td>6-12 years</td>
<td>0.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>

5.3 Preclinical safety data

Preclinical 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 study of piperacillin/tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs following i.p. administration to rats. Fertility of the F1 generation and embryonic development of the F2 generation was not impaired. A teratogenicity study in rats, did not show teratogenic effects after i.v. administration. In the rat, effects on the embryonic development were observed at maternal toxic doses. Peri/postnatal development was impaired (reduced fetal weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after i.p. administration in the rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

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

Piperacillin/tazobactam should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer’s solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

**After reconstitution:**

Chemical and physical in-use stability has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store below 25°C.

For storage or reconstituted solution, please refer to section 6.3.

6.5 Nature and contents of container
Each cardboard carton contains 1 vial of Type II 50 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial ; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution Directions

Intravenous Injection
Each vial of piperacillin/tazobactam 4.5 g (piperacillin 4000 mg/tazobactam 500 mg) should be reconstituted with 20 ml of one of the following diluents.

- Sterile Water for Injection
- 0.9% Sodium Chloride for Injection

Swirl until dissolved.

Intravenous Infusion
Each vial of piperacillin/tazobactam 4.5 g (piperacillin 4000 mg/tazobactam 500 mg) should be reconstituted with 20 ml of one of the above diluents. The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with Dextrose 5% in Water.

Displacement Volume
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml.

4.5 g piperacillin/tazobactam (piperacillin 4000 mg/tazobactam 500 mg) will displace 3.15 ml

For single use only. Discard any unused solution.

The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

PIPERACILLIN/TAZOBACTAM 2 G/0.25 G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
(Piperacillin as sodium salt 2000mg and Tazobactam as sodium salt 250mg)

Please read all of this leaflet carefully before you start to use this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is and what it is used for
2. Before you are given Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion
3. How Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is given
4. Possible side effects
5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion
6. Further information

1. What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is and what it is used for

Piperacillin belongs to the group of medicines known as 'broad spectrum antibiotics'. Antibiotics are used to kill the bacteria ('germs') which cause infection. Piperacillin can kill many kinds of bacteria. Tazobactam can prevent some bacteria becoming resistant to the effects of piperacillin. This means that some bacteria, which are not normally killed by piperacillin, are killed when piperacillin and tazobactam are given together.

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is used to treat adults, including the elderly, with bacterial infections such as those affecting your chest, urinary tract, blood, abdomen or skin.

Piperacillin/Tazobactam may also be used to treat infections in adults and children aged 2 to 12, who are unable to fight infections normally due to low white cell counts.

2. Before you are given Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion

Do not use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion:
If you are allergic (hypersensitive) to piperacillin or tazobactam, or if you have had allergic reactions to antibiotics known as penicillins or cephalosporins, or to medicines called beta-lactamase inhibitors (ask your doctor if you are not sure).

Take special care with Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion:
- If you have allergies. If you have several allergies make sure you tell your doctor or nurse before receiving this product.
- If you are pregnant, think you may be pregnant or are breast-feeding.
- If you have had persistent diarrhoea or colitis infection.
- If you have kidney or liver problems, or are receiving haemodialysis treatment. Your doctor may check how well your kidneys are working before you are given this medicine and you may have regular check ups whilst taking your medicine.
- If you have low levels of potassium in your blood or you are taking diuretics for heart problems or high blood pressure. Ask your doctor if you are not sure. Your doctor might take a blood sample from time to time for testing.
- If you are on a low sodium diet.
- If you are suffering from cystic fibrosis (a hereditary disease in which lungs, intestines and pancreas become clogged with thick mucus, causing respiratory and digestive problems) as piperacillin therapy has been associated with an increased risk of fever and rash in cystic fibrosis patients.
- If you are being prescribed this therapy for longer duration. Your doctor may want to perform regular blood tests during the treatment.
- If you are given higher than recommended doses intravenously (directly into a vein), you may suffer from seizure or convulsion.
- If you have had abnormality of blood coagulation (a complex process by which blood forms clots). If you have kidney problems, there are more chances of you being suffered by the blood coagulation abnormality.
- If your child is aged 12 years or under. Not all infections in children may be treated with Piperacillin/Tazobactam.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may interact with piperacillin and tazobactam. These include:
- Probenecid (for gout). This can increase the time it takes for piperacillin and tazobactam to leave your body.
- Medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).
- Methotrexate (for cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.
- Medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.
- Antibiotics including aminoglycoside. If you are given piperacillin/tazobactam in combination with an aminoglycoside, the two drugs should not be given together in the same syringe or drip.
- Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.
- Lactated Ringer’s solution is not compatible with piperacillin/tazobactam.
- Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

**Pregnancy and breast feeding**

If you are pregnant, think you may be pregnant or are trying for a baby, tell your doctor or nurse before receiving this product.

Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are pregnant or breast feeding, your doctor will decide whether Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is right for you.

Ask your doctor or pharmacist before taking any medicine.

**Driving and using machines**

No studies on the effects on the ability to drive and use machines have been performed. However, side effects could occur which may influence your ability to drive or use machines (see section 4).

**Important information about some of the ingredients of this product**

This medicinal product contains 4.72 mmol (109 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into consideration if you are on a controlled sodium diet.

3. **How Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion is given**

Your doctor will give your medicine to you by slow injection (for 3-5 minutes) or through a drip (for 20-30 minutes) into one of your veins. The dose of medicine given to you depends on what you are being treated for, your age, and whether or not you have kidney problems.

**Adults and children aged over 12 years**

The usual dose for adults and children over 12 years is 4 g/0.5 g piperacillin/tazobactam given every 8 hours. However, your doctor will decide on the exact dose depending on the severity of your infection.

In adults and children over 12 years, who are unable to fight infections normally due to low white cell counts, the usual dose is 4 g/0.5 g piperacillin/tazobactam given every 6 hours at the same time as another antibiotic called an aminoglycoside, which is given into one of your veins. The two medicines should be given in separate syringes or drips.

**Children aged 2 to 12 years**

In children aged 2 to 12 years, who are unable to fight infections normally due to low white cell counts, piperacillin/tazobactam may be used in combination with another drug called an "aminoglycoside". In this case, the usual dose is 4 g/0.5 g piperacillin/tazobactam every 6 hours. However, your doctor may calculate the dose depending on your child’s weight. (The usual dose for children weighing less than 40 kg is 90 mg per kg of body weight every 6 hours, up to the adult dose).

The two drugs (piperacillin/tazobactam in combination with an aminoglycoside) should not be given together in the same syringe or drip.
Children under 2 years of age
Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

If you are an elderly
Piperacillin/tazobactam may be used at the same dose levels as adults if you don't suffer from kidney problems.

If you are an elderly and have kidney problems, your doctor may need to reduce the dose of your medicine or adjust how often it is given.

If you have kidney problems
If you have kidney problems, your doctor may need to reduce the dose of your medicine or adjust how often it is given. Your doctor may also wish to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

If you have liver problems
No dose adjustment is necessary if you suffer from liver problems. Your doctor may wish to test your blood to make sure that your treatment is working.

Duration of Therapy
You will be given Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion until the signs of infection have disappeared and then treatment will usually be continued for a further 48 hours to make sure that the infection has gone completely.

If you are given more Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion than you should
As you will be given Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion by a doctor or nurse, you are unlikely to be given the wrong dose. However, if you experience bad side effects such as feeling sick (nausea), being sick (vomiting), diarrhoea (loose stools) and convulsions (in presence of renal failure) or think you have been given too much, tell your doctor immediately.

If you miss a dose of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion
If you think you have not been given a dose of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion, tell your doctor immediately.

If you have any further questions on the use of this product, ask your doctor or healthcare professional.

4. Possible side effects

Like all medicines, Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion can cause side effects, although not everybody gets them.

Adverse reactions have been ranked as per the seriousness of the side effect and further under headings of frequency. The following convention has been used for determining frequency:
- Very common (reported by more than 1 in 10 patients)
• Common (reported by more than 1 in 100, but less than 1 in 10 patients)
• Uncommon (reported by more than 1 in 1000, but less than 1 in 100 patients)
• Rare (reported by more than 1 in 10,000, but less than 1 in 1000 patients)
• Very rare (reported by less than 1 in 10,000 patients)
• Not known (cannot be estimated from the available data)

The following side-effects may occur:

Very serious side effects
If any of the following happen, stop taking Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion and tell your doctor immediately or go to the casualty department at your nearest hospital.

Reported rarely
• Severe allergic reaction (sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat), severe persistent bloody diarrhoea.

Reported very rarely
• Widespread redness of the skin, severe peeling of the skin or severe ulceration of the skin, eyes, mouth, nose and genitals. It may be a manifestation of Stevens-Johnson Syndrome
• Detachment of the top layer of skin from the lower layers of the skin all over the body, leaving large areas that look scalded. The loss of skin causes fluids and salts to ooze from the raw, damaged areas which can easily become infected. It may be a manifestation of Toxic epidermal necrolysis.

Serious side effects
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Reported uncommonly
• Jaundice (yellowing of the skin or whites of the eyes)
• Low blood pressure (felt as light-headedness)
• Inflammation of the veins (felt as tenderness or redness in the affected area)
• Changes in results of blood tests of kidney (e.g. increased creatinine levels in blood)
• Changes in results of blood tests of liver function (i.e. increased alanine aminotransferase and aspartate aminotransferase)
• Changes in the number of cells in the blood (red cells, white cells and platelets)

Reported rarely
• Unusual bruising and bleeding. Increase in time for your blood to clot
• Convulsions or twitching
• Blistering of the skin along with itching and rashes. It may be a manifestation of Bullous dermatitis
• Itchy lesion surrounded by pale red rings, symmetrically arranged and located on the upper body, legs, arms, palms, hands, or feet. It may be a manifestation of erythema multiforme
• Interstitial nephritis (inflammation of the cells that are between the filtering units in the kidneys)
• Renal failure (a situation in which the kidneys fail to function adequately)
• Water retention (seen as swollen hands, ankles or feet)
• Increase in levels of liver enzymes (i.e. increased alkaline phosphatase and gamma-glutamyltransferase) or bilirubin
• Hepatitis (inflammation of the liver caused by a virus or a toxin)

**Reported very rarely:**
• Low blood glucose levels which may make you confused and shaky
• Reduced blood concentration of potassium which can cause muscle weakness, twitching or abnormal heart rhythm

**Other side effects**
Tell your doctor if you notice any of the following:

**Reported commonly**
• Feeling sick (nausea)
• Being sick (vomiting)
• Diarrhoea (loose stools)
• Rash

**Reported uncommonly**
• Mouth ulcers
• Itching
• Hives (urticaria)
• Fever
• Thrush
• Mild allergic reactions
• Headache
• Difficulty sleeping
• Constipation
• Indigestion problems (dyspepsia)
• Swelling or redness around the injection site
• Stomatitis (inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, throat and roof or floor of the mouth.)

**Reported rarely**
• Weakness
• Hallucinations (a sensory perception of something that does not exist)
• Dry mouth
• Abdominal pain
• Increased Sweating
• Joint and muscle pain
• Tiredness
• Flushed red skin
• Severe shivering

If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor.
5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion

The hospital pharmacy will ensure that Piperacillin/Tazobactam is not stored above 25°C and that it is used before the expiry date printed on the label.

Made up solutions prepared in sterile conditions may be stored for up to 48 hours in a refrigerator (2–8°C).

6. Further information

What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion contains:

- The active substances are Piperacillin sodium, equivalent to 2 g of piperacillin and Tazobactam sodium, equivalent to 0.25 g of tazobactam.
- There are no other ingredients.

What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion looks like and the contents of the pack

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion comes in packs containing one small bottle of powder which must be dissolved into a solution before it is given to you by injection or infusion (a slow injection or ‘drip’) into your vein.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder
Raabaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

Manufacturer
Laboratory Reig Jofre SA
C/ Jarna S/n Pol Ind
45007, Toledo
Spain

This leaflet was last approved in 03/2010
PACKAGE LEAFLET: INFORMATION FOR THE USER

PIPERACILLIN/TAZOBACTAM RBX 4 g/0.5 g POWDER FOR SOLUTION FOR INJECTION OR INFUSION
(Piperacillin as sodium salt 4000mg and Tazobactam as sodium salt 500mg)

Please read all of this leaflet carefully before you start to use this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is and what it is used for
2. Before you are given Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion
3. How Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is given
4. Possible side effects
5. How to store Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion
6. Further information

1. What Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is and what it is used for

Piperacillin belongs to the group of medicines known as ‘broad spectrum antibiotics’. Antibiotics are used to kill the bacteria (‘germs’) which cause infection. Piperacillin can kill many kinds of bacteria. Tazobactam can prevent some bacteria becoming resistant to the effects of piperacillin. This means that some bacteria, which are not normally killed by piperacillin, are killed when piperacillin and tazobactam are given together.

Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is used to treat adults, including the elderly, with bacterial infections such as those affecting your chest, urinary tract, blood, abdomen or skin.

Piperacillin/Tazobactam RBX may also be used to treat infections in adults and children aged 2 to 12, who are unable to fight infections normally due to low white cell counts.

2. Before you are given Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion
Do not use Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion:

- If you are allergic (hypersensitive) to piperacillin or tazobactam, or if you have had allergic reactions to antibiotics known as penicillins or cephalosporins, or to medicines called beta-lactamase inhibitors (ask your doctor if you are not sure).

Take special care with Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion:

- If you have allergies. If you have several allergies make sure you tell your doctor or nurse before receiving this product.
- If you are pregnant, think you may be pregnant or are breast-feeding.
- If you have had persistent diarrhoea or colon infection.
- If you have kidney or liver problems, or are receiving haemodialysis treatment. Your doctor may check how well your kidneys are working before you are given this medicine and you may have regular check ups whilst taking your medicine.
- If you have low levels of potassium in your blood or you are taking diuretics for heart problems or high blood pressure. Ask your doctor if you are not sure. Your doctor might take a blood sample from time to time for testing.
- If you are on a low sodium diet
- If you are suffering from cystic fibrosis (a hereditary disease in which lungs, intestines and pancreas become clogged with thick mucus, causing respiratory and digestive problems) as piperacillin therapy has been associated with an increased risk of fever and rash in cystic fibrosis patients.
- If you are being prescribed this therapy for longer duration, Your doctor may want to perform regular blood test during the treatment
- If you are given higher than recommended doses intravenously (directly into a vein), you may suffer from seizure or convulsion
- If you have had abnormality of blood coagulation (a complex process by which blood forms clots). If you have kidney problems, there are more chances of you being suffered by the blood coagulation abnormality
- If your child is aged 12 years or under. Not all infections in children may be treated with Piperacillin/Tazobactam RBX

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may interact with piperacillin and tazobactam. These include:

- Probenecid (for gout). This can increase the time it takes for piperacillin and tazobactam to leave your body.
- Medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).
- Methotrexate (for cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.
- Medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.
- Antibiotics including aminoglycoside. If you are given piperacillin/tazobactam in combination with an aminoglycoside, the two drugs should not be given together in the same syringe or drip.
- Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.
• Lactated Ringer's solution is not compatible with piperacillin/tazobactam.
• Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

Pregnancy and breastfeeding
If you are pregnant, think you may be pregnant or are trying for a baby, tell your doctor or nurse before receiving this product.

Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are pregnant or breast-feeding, your doctor will decide whether Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is right for you.

Ask your doctor or pharmacist before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, side effects could occur which may influence your ability to drive or use machines (see section 4).

Important information about some of the ingredients of this product
This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into consideration if you are on a controlled sodium diet.

3. How Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion is given

Your doctor will give your medicine to you by slow injection (for 3-5 minutes) or through a drip (for 20-30 minutes) into one of your veins. The dose of medicine given to you depends on what you are being treated for, your age, and whether or not you have kidney problems.

Adults and children aged over 12 years
The usual dose for adults and children over 12 years is 4 g/0.5 g piperacillin/tazobactam given every 8 hours. However, your doctor will decide on the exact dose depending on the severity of your infection.

In adults and children over 12 years, who are unable to fight infections normally due to low white cell counts, the usual dose is 4 g/0.5 g piperacillin/tazobactam given every 6 hours at the same time as another antibiotic called an aminoglycoside, which is given into one of your veins. The two medicines should be given in separate syringes or drips.

Children aged 2 to 12 years
In children aged 2 to 12 years, who are unable to fight infections normally due to low white cell counts, piperacillin/tazobactam may be used in combination with another drug called an aminoglycoside. In this case, the usual dose is 4 g/0.5 g piperacillin/tazobactam every 6 hours. However, your doctor may calculate the dose depending on your child's weight. (The usual dose for children weighing less than 40 kg is 90 mg per kg of body weight every 6 hours, up to the adult dose).
The two drugs (piperacillin/tazobactam in combination with an aminoglycoside) should not be given together in the same syringe or drip.

Children under 2 years of age
Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

If you are an elderly
Piperacillin/tazobactam may be used at the same dose levels as adults if you don’t suffer from kidney problems.

If you are an elderly and have kidney problems, your doctor may need to reduce the dose of your medicine or adjust how often it is given.

If you have kidney problems
If you have kidney problems, your doctor may need to reduce the dose of your medicine or adjust how often it is given. Your doctor may also wish to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

If you have liver problems
No dose adjustment is necessary if you suffer from liver problems. Your doctor may wish to test your blood to make sure that your treatment is working.

Duration of Therapy
You will be given Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion until the signs of infection have disappeared and then treatment will usually be continued for a further 48 hours to make sure that the infection has gone completely.

If you are given more Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion than you should
As you will be given Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion by a doctor or nurse, you are unlikely to be given the wrong dose. However, if you experience bad side effects such as feeling sick (nausea), being sick (vomiting), diarrhoea (loose stools) and convulsions (in presence of renal failure) or think you have been given too much, tell your doctor immediately.

If you miss a dose of Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion
If you think you have not been given a dose of Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion, tell your doctor immediately.

If you have any further questions on the use of this product, ask your doctor or healthcare professional.

4. Possible side effects

Like all medicines, Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion can cause side effects, although not everybody gets them.
Adverse reactions have been ranked as per the seriousness of the side effect and further under headings of frequency. The following convention has been used for determining frequency:

- Very common (reported by more than 1 in 10 patients)
- Common (reported by more than 1 in 100, but less than 1 in 10 patients)
- Uncommon (reported by more than 1 in 1000, but less than 1 in 100 patients)
- Rare (reported by more than 1 in 10,000, but less than 1 in 1000 patients)
- Very rare (reported by less than 1 in 10,000 patients)
- Not known (cannot be estimated from the available data)

The following side-effects may occur:

**Very serious side effects**

If any of the following happen, stop taking Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion and tell your doctor immediately or go to the casualty department at your nearest hospital.

**Reported rarely**

- Severe allergic reaction (sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat), severe persistent bloody diarrhoea.

**Reported very rarely**

- Widespread redness of the skin, severe peeling of the skin or severe ulceration of the skin, eyes, mouth, nose and genitals. It may be a manifestation of Stevens-Johnson Syndrome
- Detachment of the top layer of skin from the lower layers of the skin all over the body, leaving large areas that look scalded. The loss of skin causes fluids and salts to ooze from the raw, damaged areas which can easily become infected. It may be a manifestation of Toxic epidermal necrolysis.

**Serious side effects**

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

**Reported uncommonly**

- Jaundice (yellowing of the skin or whites of the eyes)
- Low blood pressure (felt as light-headedness)
- Inflammation of the veins (felt as tenderness or redness in the affected area)
- Changes in results of blood tests of kidney (e.g. increased creatinine levels in blood)
- Changes in results of blood tests of liver function (i.e. increased alanine aminotransferase and aspartate aminotransferase)
- Changes in the number of cells in the blood (red cells, white cells and platelets)

**Reported rarely**

- Unusual bruising and bleeding. Increase in time for your blood to clot
- Convulsions or twitching
- Blistering of the skin along with itching and rashes. It may be a manifestation of Bullous dermatitis
- Itchy lesion surrounded by pale red rings, symmetrically arranged and located on the upper body, legs, arms, palms, hands, or feet. It may be a manifestation of erythema multiforme
If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor.

5. How to store Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion

The hospital pharmacy will ensure that Piperacillin/Tazobactam RBX is not stored above 25°C and that it is used before the expiry date printed on the label.

Made up solutions prepared in sterile conditions may be stored for up to 48 hours in a refrigerator (2-8°C).

6. Further information

What Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion contains:
- The active substances are Piperacillin sodium, equivalent to 4 g of piperacillin and Tazobactam sodium, equivalent to 0.5 g of tazobactam.
- There are no other ingredients.

What Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion looks like and the contents of the pack:

Piperacillin/Tazobactam RBX 4 g/0.5 g powder for solution for injection or infusion comes in packs containing one small bottle of powder which must be dissolved into a solution before it is given to you by injection or infusion (a slow injection or ‘drip’) into your vein.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

Manufacturer
Laboratory Reig Jofre SA
C/ Jarra S/n Pol.Ind
45007, Toledo
Spain

This leaflet was last approved in 03/2010
Module 4
Labelling

Representative wording for the product licences PL 14894/0487 and PL 14894/0488 are provided below. The label wording for all other product licences is consistent with the wording presented for these two licences.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
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</thead>
<tbody>
<tr>
<td>CARTON</td>
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</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains piperacillin sodium equivalent to 2 g piperacillin and tazobactam sodium equivalent to 0.25 g tazobactam

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for injection or infusion

1 vial

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

Do not mix or co-administer with any aminoglycoside

Do not reconstitute or dilute with Lactated Ringer's (Hartmann's) Solution

7. **OTHER SPECIAL WARNING(S) IF NECESSARY**

Use as directed by a physician.

Discard any unused solution
Contains 4.72 mmol (109 mg) of sodium per vial

8. **EXPIRY DATE**

Exp.

9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE PRODUCTS DERIVED THEREFROM (IF APPLICABLE)**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORIZATON HOLDER**

<To be completed nationally>

12. **MARKETING AUTHORIZATION NUMBER(S)**

<To be completed nationally>

13. **BATCH NUMBER**

B.N.

14. **GENERAL CLASSIFICATION FOR SUPPLY**

<To be completed nationally>

15. **INSTRUCTIONS FOR USE**

Each vial should be reconstituted with 10 ml of sterile water for injection or 0.9% sodium chloride. For intravenous infusion, the reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with dextrose 5% in water

16. **INFORMATION IN BRAILLE**
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains piperacillin sodium equivalent to 2 g piperacillin and tazobactam sodium equivalent to 0.25 g tazobactam

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

Do not mix or co-administer with any aminoglycoside.
Do not reconstitute or dilute with Lactated Ringer’s (Hartmann’s) Solution

7. OTHER SPECIAL WARNING(S) IF NECESSARY

Use as directed by a physician.
Discard any unused solution

Contains 4.72 mmol (109 mg) of sodium per vial

8. EXPIRY DATE

Exp.

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE PRODUCTS DERIVED THEREFROM (IF APPLICABLE)

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<To be completed nationally>

12. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

13. BATCH NUMBER

B.N.

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS FOR USE

Each vial should be reconstituted with 10 ml of sterile water for injection or 0.9% sodium chloride. For intravenous infusion, the reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with dextrose 5% in water.

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains piperacillin sodium equivalent to 4 g piperacillin and tazobactam sodium equivalent to 0.5 g tazobactam

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children
Do not mix or co-administer with any amnoglycoside.
Do not reconstitute or dilute with Lactated Ringer's (Hartmann's) Solution

7. OTHER SPECIAL WARNING(S) IF NECESSARY

Use as directed by a physician.

Discard any unused solution

Contains 9.44 mmol (217 mg) sodium per vial
8. EXPIRY DATE

Exp.

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE PRODUCTS DERIVED THEREFROM (IF APPLICABLE)

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<To be completed nationally>

12. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

13. BATCH NUMBER

B.N.

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS FOR USE

Each vial of should be reconstituted with 20 ml of sterile water for injection or 0.9% sodium chloride. For intravenous infusion, the reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with dextrose 5% in water.

16. INFORMATION IN BRAILLE
Piperacillin/Tazobactam 2/0.25 and 4/0.5g powder for solution for injection or infusion

MINIMUM PARTICULARS TO APPEAR ON SMALL IMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains piperacillin sodium equivalent to 4 g piperacillin and tazobactam sodium equivalent to 0.5 g tazobactam

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children
Do not mix or co-administer with any aminoglycoside.
Do not reconstitute or dilute with Lactated Ringer's (Hartmann's) Solution

7. OTHER SPECIAL WARNING(S) IF NECESSARY

Use as directed by a physician.
Discard any unused solution
Contains 9.44 mmol (217 mg) sodium per vial
8. **EXPIRY DATE**

Exp.

9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE PRODUCTS DERIVED THEREFROM (IF APPLICABLE)**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<To be completed nationally>

12. **MARKETING AUTHORISATION NUMBER(S)**

<To be completed nationally>

13. **BATCH NUMBER**

B.N.

14. **GENERAL CLASSIFICATION FOR SUPPLY**

<To be completed nationally>

15. **INSTRUCTIONS FOR USE**

Each vial of should be reconstituted with 20 ml of sterile water for injection or 0.9% sodium chloride. For intravenous infusion, the reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with dextrose 5% in water.

16. **INFORMATION IN BRAILLE**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
On 21 March 2010, Belgium, the Czech Republic, Denmark, Finland, Hungary, the Netherlands, Poland, Portugal, the Slovak Republic, Sweden and the UK agreed to grant Marketing Authorisations to Ranbaxy (UK) Limited for the medicinal products Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion (PL 14894/0487-92; UK/H/1010-2/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 24 November 2010.

Piperacillin/tazobactam is indicated for treatment of moderate to severe systemic and/or local bacterial infections in which beta-lactamase-producing bacteria are suspected or have been detected, such as:

**Adults/Adolescents and the Elderly**
- Nosocomial pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Intra-abdominal infections
- Skin and soft tissue infections
- Bacterial infections in neutropenic adults

**Children (2-12 years)**
- Bacterial infections in neutropenic children

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Czech Republic, Denmark, Finland, Hungary, the Netherlands, Poland, Portugal, the Slovak Republic and Sweden as Concerned Member States (CMS). The applications were submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Tazocilline 2 g/0.25 g and 4 g/0.5 g poudres pour solution pour perfusion (Wyeth Pharmaceuticals, France), which were first authorised in July 1992. The corresponding reference products in the UK are Tazocin 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion, which were first authorised to Cyanamid of Great Britain Limited in December 1992.

These products contain the active substances piperacillin sodium and tazobactam sodium. Piperacillin sodium is a semi-synthetic ureidopenicillin with broad spectrum anti-bacterial activity. Piperacillin exerts its bactericidal effects by binding with penicillin binding proteins (PBP) in the bacterial cell wall, leading to inhibition of wall synthesis and eventual lysis. Its clinical role has been strengthened by the addition of an irreversible β-lactamase-inhibitor (tazobactam), which protects piperacillin against enzymatic degradation from β-lactamase-producing bacteria. The combination of piperacillin and tazobactam compared to piperacillin alone has an expanded antimicrobial spectrum, which includes *Klebsiellae*, *Escherichia coli*, and *Proteus vulgaris* resistant to ampicillin, as well as beta-lactamase-producing *Staphylococcus aureus*. Piperacillin sodium/tazobactam sodium is indicated in patients with febrile neutropenia, lower respiratory tract infections, urinary tract infections, intra-abdominal infections, skin infections and septicemia.
No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

### II. ABOUT THE PRODUCT

| Names of the products in the Reference Member State | Piperacillin/Tazobactam 2 g/0.25 g powder for solution for injection or infusion  
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for injection or infusion |
<table>
<thead>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Piperacillin sodium and tazobactam sodium</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code)  | Piperacillin and enzyme inhibitor  
(ATC code: J01CR05)                                                                |
| Pharmaceutical form and strength(s)           | Powder for solution for injection or infusion  
2 g/0.25 g and 4 g/0.5 g                                                           |
| Reference numbers for the Decentralised Procedure | UK/H/1010-2/001-2/DC                                                             |
| Reference Member State (RMS)                   | United Kingdom                                                                    |
| Concerned Member States (CMS)                  | Belgium, Czech Republic, Denmark, Finland, Hungary, the Netherlands, Poland, Portugal, the Slovak Republic, Sweden |
| Marketing Authorisation Number(s)              | PL 14894/0487-91                                                                  |
| Name and address of the marketing authorisation holder | Ranbaxy (UK) Limited  
Building 4, Chiswick Park,  
566 Chiswick High Road, London, W4 5YE  
United Kingdom                                                                         |
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE - Piperacillin

INN: Piperacillin

Chemical name: 2S,5R,6R)-6-[(2R)-2-[[4-ethyl-2,3-dioxopiperazin-1-yl]carbonyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, monohydrate

Structure:

Molecular formula: C$_{23}$H$_{27}$N$_{5}$O$_{7}$S, H$_{2}$O

Molecular Mass: 535.6

Appearance: A white or almost white powder, slightly soluble in water, freely soluble in methanol, slightly soluble in ethyl acetate.

Piperacillin is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
ACTIVE SUBSTANCE - Tazobactam

INN: Tazobactam acid

Chemical name: (2S, 3S, 5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid 4,4-dioxide

Structure:

\[
\text{Structure Image}
\]

Molecular formula: \( C_{10}H_{12}N_{4}O_{5}S \)

Molecular Mass: 300.3

Appearance: A white to off-white crystalline powder, freely soluble in N,N-dimethyl formamide and very slightly soluble in water

At the time of writing this public assessment report, tazobactam acid is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
MEDICINAL PRODUCT

Other Ingredients
There are no excipients for these products.

Pharmaceutical Development
The objective of the development programme was to produce stable, efficacious products that could be considered as generic medicinal products of the UK reference products Tazocin 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion (Cyanamid of Great Britain Limited, UK) and their European equivalents.

Suitable pharmaceutical development data have been provided for these applications.

Comparable impurity profiles have been provided for these products and the UK reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished products are supplied in 20ml or 50ml Type II transparent glass vials (for the 2 g/0.25 g and 4 g/0.5 g strengths, respectively) with bromobutyl stoppers and aluminium flip-off caps. Pack sizes are 1, 50 and 100 vials.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been proposed for the powder when stored in the packaging proposed for marketing, with the storage conditions “Store below 25°C”. After reconstitution, it is stated that the solution for intravenous injection/infusion should be used immediately, from a microbiological point of view. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.
Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support these applications for parenteral products.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labelling
The SmPCs, PILs and labels are pharmaceutically acceptable.

Package leaflets have been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that these contain.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of piperacillin sodium and tazobactam sodium are well-known, no new non-clinical data have been submitted and none are required.

Non-Clinical Expert Report
The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the pharmacology and toxicology of piperacillin sodium and tazobactam sodium.

Environmental Risk Assessment
A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution of brand leaders that have been used for many years, they are not considered to increase the environmental impact or have any increased negative environmental effect; thus, no environmental risk assessment is required.

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products, in accordance with the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98).

Efficacy
No new efficacy data have been submitted and none are required for applications of this type.

Safety
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications. Piperacillin sodium and tazobactam sodium as active ingredients have a well-established and acceptable level of safety in the proposed indications.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labelling
The SmPCs, PILs and labelling are clinically acceptable. The SmPCs are consistent with those for the innovator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossiers.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.

Conclusion
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion (PL 14894/0487-92; UK/H/1010-12/001-2/DC) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new clinical data were submitted for these applications. No bioequivalence studies were submitted or required for these applications.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with piperacillin sodium and tazobactam sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/12/2011</td>
<td>Type IB Variation</td>
<td>To update sections 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 3 (Pharmaceutical form), 4 (Clinical particulars), 5 (Pharmacological properties), 6.2 (Incompatibilities), 6.3 (Shelf life), 6.4 (Special precautions for storage) and 6.6 (Special precautions for disposal) of the SmPC and consequentially the label and leaflet in accordance with Article 30 Referral EMEA/H/A-30/1149 and also the QRD template.</td>
<td>Approved – 25/04/2012</td>
</tr>
</tbody>
</table>
Annex 1

Product Licence Numbers: PL 14894/0487-0002
PL 14894/0488-0002
PL 14894/0489-0002
PL 14894/0490-0002
PL 14894/0491-0003
PL 14894/0492-0003

European Procedure Numbers: UK/H/1010/001/IB/001
UK/H/1010/002/IB/001
UK/H/1011/001/IB/001
UK/H/1011/002/IB/001
UK/H/1012/001/IB/002
UK/H/1012/002/IB/002

Product: Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion
Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion

Marketing Authorisation Holder: Ranbaxy (UK) Limited

Active Ingredient(s): Piperacillin sodium
Tazobactam sodium

Reason:
To update sections 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 3 (Pharmaceutical form), 4 (Clinical particulars), 5 (Pharmacological properties), 6.2 (Incompatibilities), 6.3 (Shelf life), 6.4 (Special precautions for storage) and 6.6 (Special precautions for disposal) of the Summary of Product Characteristics (SmPC) and consequentially the label and leaflet in accordance with Article 30 Referral EMEA/H/A-30/1149 and also the QRD template.

Supporting Evidence
In these Mutual Recognition (MR) Type II standard variation applications, the applicant has proposed changes to Sections 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 3 (Pharmaceutical form), 4 (Clinical particulars), 5 (Pharmacological properties), 6.2 (Incompatibilities), 6.3 (Shelf life), 6.4 (Special precautions for storage) and 6.6 (Special precautions for disposal) of the SmPCs, the PIL and the labelling in accordance with Article 30 Referral EMEA/H/A-30/1149 and also the QRD template.
The applicant has submitted:
– Existing and proposed SmPCs
– Existing and proposed PILs
– Existing and proposed labels

Evaluation
The proposed SmPCs, PILs and labelling provided by the MAH are satisfactory.
THE FINAL APPROVED SMPCS, PILS AND LABELLING ARE PRESENTED BELOW:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each vial contains piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.

   Each vial contains 108 mg of sodium.

3. PHARMACEUTICAL FORM
   Powder for solution for infusion.
   White or off-white powder.

4. CLINICAL PARTICULARS

   4.1. Therapeutic indications
   Piperacillin/Tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

   **Adults and adolescents**
   - Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
   - Complicated urinary tract infections (including pyelonephritis)
   - Complicated intra-abdominal infections
   - Complicated skin and soft tissue infections (including diabetic foot infections)

   Treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

   Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

   **Children 2 to 12 years of age**
   - Complicated intra-abdominal infections

   Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

   Consideration should be given to official guidance on the appropriate use of antibacterial agents.

   4.2. Posology and method of administration

   **Posology**
   The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

   **Adult and adolescent patients**

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

   For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

   The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:
Treatment frequency | Piperacillin/Tazobactam 2 g / 0.25 g powder for solution for infusion
---|---
Every 6 hours | Severe pneumonia
Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours | Complicated urinary tract infections (including pyelonephritis)
Complicated intra-abdominal infections
Skin and soft tissue infections (including diabetic foot infections)

Renal impairment
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>Piperacillin /Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20-40</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%-50% of piperacillin in 4 hours.

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections
The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.

Renal impairment
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>Piperacillin /Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</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.
Use in children aged below 2 years
The safety and efficacy of Piperacillin/Tazobactam in children 0–2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration
The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Route of administration
Piperacillin/Tazobactam 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3. 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).

4.4. 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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 Piperacillin/Tazobactam 2 g / 0.25 g contains 4.72 mmol (108 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.
4.5. Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7. Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects
The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common ( \geq 1/100 \text{ to } &lt; 1/10 )</th>
<th>Uncommon ( \geq 1/1,000 \text{ to } &lt; 1/100 )</th>
<th>Rare ( \geq 1/10,000 \text{ to } &lt; 1/1,000 )</th>
<th>Very rare ((&lt; 1/10,000))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>candidal superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>leukopenia, neutropenia, thrombocytopenia</td>
<td></td>
<td>anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia</td>
<td>agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>hypersensitivity</td>
<td></td>
<td>anaphylactic/ anaphylactoid reaction (including shock)</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension, thrombophlebitis, phlebitis</td>
<td>flushing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea, vomiting, nausea</td>
<td>jaundice, stomatitis, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td></td>
<td>hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
<td></td>
</tr>
</tbody>
</table>
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

4.9. 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 (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>8/16</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16/16</td>
</tr>
<tr>
<td>Gram-negative and Gram-positive anaerobes</td>
<td>8/16</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4/16</td>
</tr>
</tbody>
</table>

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*<sup>x</sup>
  - *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*

### Cell wall deficient strains
- *Klebsiella pneumoniae*
- *Morganella morganii*

### INHERENTLY RESISTANT ORGANISMS

<table>
<thead>
<tr>
<th>Aerobic Gram-positive micro-organisms</th>
<th>Aerobic Gram-negative micro-organisms</th>
<th>Legionella species</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Corynebacterium jeikeium</em></td>
<td><em>Legionella species</em></td>
<td></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other microorganisms
- *Chlamydophila 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.

### 5.2. 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 which has been found to be micro-biologically 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 reduce the rate of elimination 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.

### 5.3. Preclinical safety data

Preclinical 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 the F2 generation was 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.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

None.

#### 6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.
Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann’s) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

**6.3. Shelf life**

Unopened vial: 2 years

*Reconstituted solution in vial*

Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

*Diluted infusion solution*

After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

**6.4. Special precautions for storage**

Unopened vials: Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

Each cardboard carton contains 1 vial of Type II 20 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

**6.6. Special precautions for disposal and handling**

The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

*Intravenous use*

Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tacobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tacobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
  * 0.9% (9 mg/ml) sodium chloride solution for injection
  * Sterile water for injections
  * Glucose 5%
The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as
directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and
tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with
one of the following compatible solvents:

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Sterile water for injections
- Dextran 6% in 0.9% sodium chloride

Displacement Volume
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml.

2.25 g piperacillin/tazobactam (piperacillin 2000 mg/tazobactam 250 mg) will displace 1.58 ml.

See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0487

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/11/2010

10 DATE OF REVISION OF THE TEXT
25/04/2012
1. **NAME OF THE MEDICINAL PRODUCT**
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each vial contains piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.

Each vial contains 217 mg of sodium.

3. **PHARMACEUTICAL FORM**
Powder for solution for infusion.
White or off-white powder.

4. **CLINICAL PARTICULARS**
4.1. **Therapeutic indications**
Piperacillin/Tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

*Adults and adolescents*
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including 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.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

*Children 2 to 12 years of age*
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. **Posology and method of administration**

*Posology*
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

*Adult and adolescent patients*

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

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

<table>
<thead>
<tr>
<th>Treatment frequency</th>
<th>Piperacillin/Tazobactam 2 g / 0.25 g powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropenic 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>
Renal impairment
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>Piperacillin / Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20</td>
<td>Maximum dose suggested: 4 g / 0.5 g every 12 hours</td>
</tr>
<tr>
<td>≥ 20-40</td>
<td>Maximum dose suggested: 4 g / 0.5 g every 8 hours</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</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%-50% of piperacillin in 4 hours.

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections
The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.

Renal impairment
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>Piperacillin / Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50</td>
<td>70 mg piperacillin / 8.75 mg tazobactam / kg every 8 hours.</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>No dose adjustment needed.</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.

Use in children aged below 2 years
The safety and efficacy of Piperacillin/Tazobactam in children 0-2 years of age has not been established.

No data from controlled clinical studies are available.
**Treatment duration**
The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

**Route of administration**
Piperacillin/Tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

### 4.3. 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).

### 4.4. 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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 abnormally 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 Piperacillin/Tazobactam 4 g / 0.5 g contains 9.44 mmol (217 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.

### 4.5. Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7. Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects
The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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.

<table>
<thead>
<tr>
<th>System Organ Class</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>Very rare (≤ &lt;= 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>candidal superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>leukopenia, neutropenia,</td>
<td></td>
<td>anemia, haemolytic anaemia,</td>
<td>agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
<td></td>
<td>purpura, epistaxis, bleeding time prolonged, eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>hypersensitivity</td>
<td></td>
<td>anaphylactic/ anaphylactoid reaction (including shock)</td>
<td>hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension, thrombophlebitis, phlebitis</td>
<td></td>
<td>flushing</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea, vomiting, nausea</td>
<td>jaundice, stomatitis, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td>hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, including maculopapular rash</td>
<td>urticaria, pruritus</td>
<td>erythema multiforme, dermatitis bullous, exanthema</td>
<td>toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td>arthralgia,</td>
<td></td>
</tr>
</tbody>
</table>
and connective tissue disorders | myalgia
---|---
Renal and urinary disorders | blood creatinine increased | renal failure, tubulointerstitial nephritis | blood urea increased
General disorders and administration site conditions | pyrexia, injection-site reaction | chills

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

4.9. 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 (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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 (PBP), 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>8/16</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16/16</td>
</tr>
<tr>
<td>Gram-negative and Gram-positive anaerobes</td>
<td>8/16</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4/16</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>COMMONLY SUSCEPTIBLE SPECIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Staphylococcus aureus, methicillin-susceptible$^4$</td>
</tr>
<tr>
<td>Staphylococcus species, coagulase negative, methicillin-susceptible</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Group B streptococci</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Citrobacter koseri</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Clostridium species</td>
</tr>
<tr>
<td>Eubacterium species</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis group</td>
</tr>
<tr>
<td>Fusobacterium species</td>
</tr>
<tr>
<td>Porphyromonas species</td>
</tr>
<tr>
<td>Prevotella species</td>
</tr>
<tr>
<td><strong>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecium$^{5,6}$</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
</tr>
<tr>
<td>Streptococcus viridans group</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Acinetobacter baumannii$^8$</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Enterobacter species</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
</tr>
<tr>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>Providencia ssp.</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
</tr>
</tbody>
</table>

**Serratia species**

**INHERENTLY RESISTANT ORGANISMS**

- Aerobic Gram-positive micro-organisms
  - Corynebacterium jeikeium
- Aerobic Gram-negative micro-organisms
  - Legionella species
  - Stenotrophomonas maltophilia

**Other microorganisms**

- Chlamyphilia pneumonia
- Mycoplasma pneumonia

*S 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.

### 5.2. 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 which has been found to be micro-biologically 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 reduce the rate of elimination 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.

5.3. Preclinical safety data
Preclinical 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 the F2 generation was 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2. Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.
Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer’s (Hartmann’s) solution is not compatible with piperacillin/tazobactam.

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

6.3. Shelf life
Unopened vial: 2 years

Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution
After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage
Unopened vials: Do not store above 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Each cardboard carton contains 1 vial of Type II 50 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial ; 50 vials (clinical package); 100 vials (clinical package).
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tacobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tacobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
  * 0.9% (9 mg/ml) sodium chloride solution for injection
  * Sterile water for injections
  * Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.
The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

- 0.9\% (9 mg/ml) sodium chloride solution for injection
- Glucose 5\%
- Sterile water for injections
- Dextran 6\% in 0.9\% sodium chloride

*Displacement Volume*

Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml.

4.5 g piperacillin/tazobactam (piperacillin 4000 mg/tazobactam 500 mg) will displace 3.15 ml.

See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0488

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/11/2010

10 DATE OF REVISION OF THE TEXT
25/04/2012
1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.

Each vial contains 108 mg of sodium.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Piperacillin/Tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including 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.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

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

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

<table>
<thead>
<tr>
<th>Treatment frequency</th>
<th>Piperacillin/Tazobactam 2 g / 0.25 g powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropenic 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>
Renal impairment
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>Piperacillin/Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20-40</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%-50% of piperacillin in 4 hours.

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)
Infections
The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

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

Renal impairment
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>Piperacillin /Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</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.

Use in children aged below 2 years
The safety and efficacy of Piperacillin/Tazobactam in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration
The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Route of administration
Piperacillin/Tazobactam 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 **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).

4.4 **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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 Piperacillin/Tazobactam 2 g / 0.25 g contains 4.72 mmol (108 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.

4.5 **Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects

The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common $\geq 1/100$ to $&lt; 1/10$</th>
<th>Uncommon $\geq 1/1,000$ to $&lt; 1/100$</th>
<th>Rare $\geq 1/10,000$ to $&lt; 1/1,000$</th>
<th>Very rare ($&lt; 1/10,000$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>candidal superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>leukopenia, neutropenia, thrombocytopenia</td>
<td>anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia</td>
<td>agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>hypersensitivity</td>
<td>anaphylactic/anaphylactoid reaction (including shock)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension, thrombophlebitis, phlebitis</td>
<td>flushing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea, vomiting, nausea</td>
<td>jaundice, stomatitis, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td>hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, including maculopapular rash</td>
<td>urticaria, pruritus</td>
<td>erythema multiforme, dermatitis bullous, exanthema</td>
<td>toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>arthralgia, myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>blood creatinine increased</td>
<td>renal failure, tubulointerstitial nephritis</td>
<td>blood urea increased</td>
<td></td>
</tr>
<tr>
<td>General disorders and</td>
<td>pyrexia, injection-site</td>
<td>chills</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Piperacillin/Tazobactam therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

4.9 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
</tr>
</thead>
</table>
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

<table>
<thead>
<tr>
<th>COMMONLY SUSCEPTIBLE SPECIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin-susceptible</td>
</tr>
<tr>
<td><em>Staphylococcus</em> species, <em>coagulase negative</em>, methicillin-susceptible</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><em>Group B streptococci</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><strong>Anaerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Clostridium</em> species</td>
</tr>
<tr>
<td><em>Eubacterium</em> species</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> species</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> group</td>
</tr>
<tr>
<td><em>Fusobacterium</em> species</td>
</tr>
<tr>
<td><em>Porphyromonas</em> species</td>
</tr>
<tr>
<td><em>Prevotella</em> species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em> group</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Providencia ssp.</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>*<em>Serratia</em> species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INHERENTLY RESISTANT ORGANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Corynebacterium jeikeium</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Legionella</em> species</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td><em>Chlamydia pneumonia</em></td>
</tr>
</tbody>
</table>
5.2 Pharmacokinetic properties

Absorption
The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 $\mu$g/ml and 34 $\mu$g/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 which has been found to be micro-biologically 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 reduce the rate of elimination 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.

### 5.3 Preclinical safety data
Preclinical 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 the F2 generation was 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.

### 6 PHARMACEUTICAL PARTICULARS
#### 6.1 List of excipients
None.

#### 6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann’s) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

#### 6.3 Shelf life
Unopened vial: 2 years
Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution
After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).
From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 **Special precautions for storage**
Unopened vials: Do not store above 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 **Nature and contents of container**
Each cardboard carton contains 1 vial of Type II 20 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial; 50 vials (clinical package); 100 vials (clinical package).
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

**Intravenous use**
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

*Compatible solvents for reconstitution:*
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections
- Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Sterile water for injections
- Dextran 6% in 0.9% sodium chloride

**Displacement Volume**
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml. 2.25 g piperacillin/tazobactam (piperacillin 2000 mg/tazobactam 250 mg) will displace 1.58 ml.

See section 6.2 for incompatibilities.
Any unused product or waste material should be disposed of in accordance with local requirements.
For single use only. Discard any unused solution.

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
    PL 14894/0489

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
    24/11/2010

10 DATE OF REVISION OF THE TEXT
    25/04/2012
1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.

Each vial contains 217 mg of sodium.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Piperacillin/Tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including 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.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

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

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

<table>
<thead>
<tr>
<th>Treatment frequency</th>
<th>Piperacillin/Tazobactam 4 g / 0.5 g powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropenic 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>
Renal impairment

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>Piperacillin / Tazobactam 4 g / 0.5 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20–40</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%-50% of piperacillin in 4 hours.

Hepatic impairment

No dose adjustment is necessary (see section 5.2).

Dose in elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)
Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

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

Renal impairment

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>Piperacillin / Tazobactam 4 g / 0.5 g powder for solution for infusion (recommended dose)</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.

Use in children aged below 2 years

The safety and efficacy of Piperacillin/Tazobactam in children 0-2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.
Route of administration
Piperacillin/Tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 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).

4.4 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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 Piperacillin/Tazobactam 4 g / 0.5 g contains 9.44 mmol (217 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.

4.5 Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin/tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects

The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1000 to &lt; 1/100</th>
<th>Rare ≥ 1/10,000 to &lt; 1/1,000</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td>candidial superinfection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>leukopenia, neutropenia, thrombocytopenia</td>
<td></td>
<td>anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia</td>
<td>agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>hypersensitivity</td>
<td>anaphylactic/ anaphylactoid reaction (including shock)</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>headache, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>hypotension, thrombophlebitis, phlebitis</td>
<td>flushing</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea, vomiting, nausea</td>
<td>jaundice, stomatitis, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td>hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, including maculopapular rash</td>
<td>urticaria, pruritus</td>
<td>erythema multiforme, dermatitis bullous, exanthema</td>
<td>toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td>arthralgia, myalgia</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>blood creatinine increased</td>
<td>renal failure, tubulointerstitial nephritis</td>
<td>blood urea increased</td>
<td></td>
</tr>
</tbody>
</table>
disorders and administration site conditions | injection-site reaction
--- | ---
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

4.9 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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
### 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.

<table>
<thead>
<tr>
<th>Groupings of relevant species according to piperacillin / tazobactam susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY SUSCEPTIBLE SPECIES</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Staphylococcus aureus, methicillin-susceptible</td>
</tr>
<tr>
<td>Staphylococcus species, coagulase negative, methicillin-susceptible</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Group B streptococci</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Citrobacter koseri</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Clostridium species</td>
</tr>
<tr>
<td>Eubacterium species</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis group</td>
</tr>
<tr>
<td>Fusobacterium species</td>
</tr>
<tr>
<td>Porphyromonas species</td>
</tr>
<tr>
<td>Prevotella species</td>
</tr>
<tr>
<td><strong>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecium$^{\text{+++}}$</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
</tr>
<tr>
<td>Streptococcus viridans group</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Acinetobacter baumannii$^S$</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>Enterobacter species</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
</tr>
<tr>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>Providencia ssp.</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td><strong>Serratia species</strong></td>
</tr>
<tr>
<td><strong>INHERENTLY RESISTANT ORGANISMS</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td>Corynebacterium jeikeium</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td>Legionella species</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia$^{\text{++}}$</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td>Chlamydia pneumonia</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
</tr>
</tbody>
</table>

$^S$ Species showing natural intermediate susceptibility.

$^{\text{+++}}$ Species for which high-resistance rates (more than 50%) have been observed in one or more
Piperacillin/Tazobactam 2/0.25 and 4/0.5g powder for solution for injection or infusion  UK/H/1010-2/001-2/DC

5.2 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 tissue 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 which 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 reduce the rate of elimination 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.

5.3 Preclinical safety data
Preclinical 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 the F2 generation was 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer’s solution is not compatible with piperacillin/tazobactam.

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

6.3 Shelf life
Unopened vial: 2 years

Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution
After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.
6.4 Special precautions for storage
Unopened vials: Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Each cardboard carton contains 1 vial of Type II 50 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

 Marketable pack sizes: 1 vial; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections
- Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Sterile water for injections
- Dextran 6% in 0.9% sodium chloride

Displacement Volume
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml. 4.5 g piperacillin/tazobactam (piperacillin 4000 mg/tazobactam 500 mg) will displace 3.15 ml. See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 MARKETING AUTHORITYHOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom
<table>
<thead>
<tr>
<th></th>
<th>MARKETING AUTHORISATION NUMBER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>PL 14894/0490</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>24/11/2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DATE OF REVISION OF THE TEXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>25/04/2012</td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.

Each vial contains 108 mg of sodium.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Piperacillin/tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including 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.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients
Infections
The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

<table>
<thead>
<tr>
<th>Treatment frequency</th>
<th>Piperacillin/Tazobactam 2 g / 0.25 g powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropenic 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>
Renal impairment

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>Piperacillin / Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20-40</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%-50% of piperacillin in 4 hours.

Hepatic impairment

No dose adjustment is necessary (see section 5.2).

Dose in elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

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

Renal impairment

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>Piperacillin / Tazobactam 2 g / 0.25 g powder for solution for infusion (recommended dose)</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.

Use in children aged below 2 years

The safety and efficacy of Piperacillin/Tazobactam in children 0-2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Route of administration

Piperacillin/Tazobactam 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.
4.3 **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).

4.4 **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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 Piperacillin/Tazobactam 2 g / 0.25 g contains 4.72 mmol (108 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.

4.5 **Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.
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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1000 to &lt; 1/100</th>
<th>Rare ≥ 1/10,000 to &lt; 1/1000</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>candida superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>candida superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>candida superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>candida superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>anaphylactic/anaphylactoid reaction (including shock)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Headache, insomnia</td>
<td></td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
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<tr>
<td>Hypertension, thrombophlebitis, phlebitis</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diarrhoea, vomiting, nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jaundice, stomatitis, constipation, dyspepsia</td>
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<td></td>
<td></td>
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<tr>
<td>Pseudo-membranous colitis, abdominal pain</td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
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<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rash, including maculopapular rash</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Urticaria, pruritus</td>
<td>erythema multifforme, dermatitis bullous, exanthema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia, myalgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>renal failure, tubulointerstitial nephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia, injection-site reaction</td>
<td>Chills</td>
<td></td>
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</tr>
</tbody>
</table>
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

4.9 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>8/16</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16/16</td>
</tr>
<tr>
<td>Gram-negative and Gram-positive anaerobes</td>
<td>8/16</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4/16</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Groupings of relevant species according to piperacillin / tazobactam susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY SUSCEPTIBLE SPECIES</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin-susceptible*</td>
</tr>
<tr>
<td><em>Staphylococcus</em> species, coagulase negative, methicillin-susceptible*</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><em>Group B streptococci</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><strong>Anaerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Clostridium</em> species</td>
</tr>
<tr>
<td><em>Eubacterium</em> species</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> species</td>
</tr>
<tr>
<td><strong>Anaerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> group</td>
</tr>
<tr>
<td><em>Fusobacterium</em> species</td>
</tr>
<tr>
<td><em>Porphyromonas</em> species</td>
</tr>
<tr>
<td><em>Prevotella</em> species</td>
</tr>
<tr>
<td><strong>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecium</em>§</td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans group</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em>§</td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Providencia ssp.</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Serratia</em> species</td>
</tr>
<tr>
<td><strong>INHERENTLY RESISTANT ORGANISMS</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Corynebacterium jeikeium</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Legionella</em> species</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em>§</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td><em>Chlamydophila pneumonia</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumonia</em></td>
</tr>
</tbody>
</table>

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.
5.2 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 tissue 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 which has been found to be micro-biologically 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 reduce the rate of elimination 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.
5.3  **Preclinical safety data**

Preclinical 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 the F2 generation was 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.

6  **PHARMACEUTICAL PARTICULARS**

6.1  **List of excipients**

None.

6.2  **Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann’s) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

6.3  **Shelf life**

Unopened vial: 2 years

Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution
After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4  **Special precautions for storage**

Unopened vials: Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 Nature and contents of container
Each cardboard carton contains 1 vial of Type II 20 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial, 10 vials, 12 vials; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Sterile water for injections
  - Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Glucose 5%
  - Sterile water for injections
  - Dextran 6% in 0.9% sodium chloride

Displacement Volume
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml. 2.25 g piperacillin/tazobactam (piperacillin 2000 mg/tazobactam 250 mg) will displace 1.58 ml.

See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements. For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0491

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/11/2010
10 DATE OF REVISION OF THE TEXT
25/04/2012
1 NAME OF THE MEDICINAL PRODUCT
Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.

Each vial contains 217 mg of sodium.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Piperacillin/Tazobactam is indicated for treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including 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.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

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

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

<table>
<thead>
<tr>
<th>Treatment frequency</th>
<th>Piperacillin/Tazobactam 4 g / 0.5 g powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 hours</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td></td>
<td>Neutropenic 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>
Renal impairment
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>Piperacillin / Tazobactam 4 g / 0.5 g powder for solution for infusion (recommended dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>20-40</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%-50% of piperacillin in 4 hours.

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)
Infections
The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

<table>
<thead>
<tr>
<th>Dose per weight and treatment frequency</th>
<th>Indication / condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours</td>
<td>Neutropenic children with fever suspected to be due to bacterial infections*</td>
</tr>
<tr>
<td>100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours</td>
<td>Complicated intra-abdominal infections*</td>
</tr>
</tbody>
</table>

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

Renal impairment
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>Piperacillin / Tazobactam 4 g / 0.5 g powder for solution for infusion (recommended dose)</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.

Use in children aged below 2 years
The safety and efficacy of Piperacillin/Tazobactam in children 0-2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration
The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Route of administration
Piperacillin/Tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 **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).

4.4 **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 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 [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.

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.

Therapy with Piperacillin/Tazobactam 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 Piperacillin/Tazobactam 4 g / 0.5 g contains 9.44 mmol (217 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.

4.5 **Interaction with other medicinal products and other forms of 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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin
No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

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 Piperacillin/Tazobactam 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 Piperacillin/Tazobactam. 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 Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

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 (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects

The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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.

<table>
<thead>
<tr>
<th>System Organ Class</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>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>candidal superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>leukopenia, neutropenia, thrombocytopenia</td>
<td>anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia</td>
<td>agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>hypersensitivity</td>
<td>anaphylactic/anaphylactoid reaction (including shock)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td>hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension, thrombophlebitis, phlebitis</td>
<td>flushing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea, vomiting, nausea</td>
<td>jaundice, stomatitis, constipation, dyspepsia</td>
<td>pseudo-membranous colitis, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased</td>
<td>hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, including maculopapular rash</td>
<td>urticaria, pruritus</td>
<td>erythema multiforme, dermatitis bullous, exanthema</td>
<td>toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>blood creatinine increased</td>
<td>renal failure, tubulointerstitial nephritis</td>
<td>blood urea increased</td>
<td></td>
</tr>
<tr>
<td>General disorders and</td>
<td>pyrexia, injection-site</td>
<td>chills</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Piperacillin/Tazobactam has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

4.9 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including 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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>8/16</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16/16</td>
</tr>
<tr>
<td>Gram-negative and Gram-positive anaerobes</td>
<td>8/16</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Groupings of relevant species according to piperacillin / tazobactam susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY SUSCEPTIBLE SPECIES</strong></td>
</tr>
<tr>
<td>Aerobic Gram-positive micro-organisms</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus, methicillin-susceptible</em></td>
</tr>
<tr>
<td><em>Staphylococcus species, coagulase negative, methicillin-susceptible</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><em>Group B streptococci</em></td>
</tr>
<tr>
<td>Aerobic Gram-negative micro-organisms</td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td>Anaerobic Gram-positive micro-organisms</td>
</tr>
<tr>
<td><em>Clostridium species</em></td>
</tr>
<tr>
<td><em>Eubacterium species</em></td>
</tr>
<tr>
<td><em>Peptostreptococcus species</em></td>
</tr>
<tr>
<td>Anaerobic Gram-negative micro-organisms</td>
</tr>
<tr>
<td><em>Bacteroides fragilis group</em></td>
</tr>
<tr>
<td><em>Fusobacterium species</em></td>
</tr>
<tr>
<td><em>Porphyromonas species</em></td>
</tr>
<tr>
<td><em>Prevotella species</em></td>
</tr>
<tr>
<td><strong>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</strong></td>
</tr>
<tr>
<td>Aerobic Gram-positive micro-organisms</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans group</em></td>
</tr>
<tr>
<td>Aerobic Gram-negative micro-organisms</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Providencia ssp.</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><strong>Serratia species</strong></td>
</tr>
<tr>
<td><strong>INHERENTLY RESISTANT ORGANISMS</strong></td>
</tr>
<tr>
<td>Aerobic Gram-positive micro-organisms</td>
</tr>
<tr>
<td><em>Corynebacterium jeikeium</em></td>
</tr>
<tr>
<td>Aerobic Gram-negative micro-organisms</td>
</tr>
<tr>
<td><em>Legionella species</em></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td>Other microorganisms</td>
</tr>
<tr>
<td><em>Chlamydia pneumonia</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumonia</em></td>
</tr>
</tbody>
</table>

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.

5.2 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 tissue 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 which has been found to be micro-biologically 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 reduce the rate of elimination 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.

5.3 Preclinical safety data
Preclinical 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 the F2 generation was 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann’s) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

6.3 Shelf life
Unopened vial: 2 years

Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 24 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution
After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.
6.4 **Special precautions for storage**
Unopened vials: Do not store above 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 **Nature and contents of container**
Each cardboard carton contains 1 vial of Type II 50 ml transparent glass vial with a bromobutyl stopper and aluminium flip off cap, self adhesive identification label and a leaflet. It is also available as a bulk of 50 vials and 100 vials for hospital use only.

Marketable pack sizes: 1 vial; 10 vials, 12 vials; 50 vials (clinical package); 100 vials (clinical package).
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

**Intravenous use**
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Sterile water for injections
  - Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Glucose 5%
  - Sterile water for injections
  - Dextran 6% in 0.9% sodium chloride

**Displacement Volume**
Each gram of piperacillin/tazobactam lyophilised powder has a displacement volume of 0.7 ml. 4.5 g piperacillin/tazobactam (piperacillin 4000 mg/tazobactam 500 mg) will displace 3.15 ml.

See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road, London, W4 5YE
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0492

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/11/2010

10 DATE OF REVISION OF THE TEXT
25/04/2012
PATIENT INFORMATION LEAFLET

Package leaflet: Information for the user

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet
1. What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is and what it is used for
2. What you need to know before you use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion
3. How to use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion
4. Possible side effects
5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion
6. Contents of the pack and other information

1. What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is and what it is used for

Piperacillin belongs to the group of medicines known as “broad-spectrum penicillin antibiotics”. It can kill many kinds of bacteria. Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion can prevent some resistant bacteria from surviving the effects of piperacillin. This means that when piperacillin and tazobactam are given together, more types of bacteria are killed.

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is used in adults and adolescents to treat bacterial infections, such as those affecting the lower respiratory tract (lungs), urinary tract (kidneys and bladder), abdomen, skin or blood. Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is used in children aged 2-12 years to treat infections of the abdomen such as appendicitis, peritonitis (infection of the fluid and lining of the abdominal organs), and gallbladder (biliary) infections.

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

In certain serious infections, your doctor may consider using Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion in combination with other antibiotics.

2. What you need to know before you use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

Do not use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion:
If you are allergic to piperacillin or tazobactam, or any of the other ingredients of this medicine (listed in section 6)

If you are allergic to antibiotics known as penicillins, cephalosporins or other beta-lactamase inhibitors, as you may be allergic to Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

If you have allergies. If you have several allergies, make sure you tell your doctor or other healthcare professional before receiving this product.

If you are suffering from diarrhoea before, or if you develop diarrhoea during or after your treatment. In this case, make sure you tell your doctor or other healthcare professional immediately. Do not take any medicine for the diarrhoea without first checking with your doctor.

If you have low levels of potassium in your blood. Your doctor may want to check your kidneys before you take this medicine and may perform regular blood tests during treatment.

If you have kidney or liver problems, or are receiving haemodialysis. Your doctor may want to check your kidneys before you take this medicine, and may perform regular blood tests during treatment.

If you are taking certain medicines (called anticoagulants) to avoid an excess of blood clotting (see also Other medicines and Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion in this leaflet) or any unexpected bleeding occurs during the treatment. In this case, you should inform your doctor or other healthcare professional immediately.

If you develop convulsions during the treatment. In this case, you should inform your doctor or other healthcare professional.

If you think you developed a new or worsening infection. In this case, you should inform your doctor or other healthcare professional.

**Children below 2 years**
Piperacillin / tazobactam is not recommended for use in children below the age of 2 years due to insufficient data on safety and effectiveness.

**Other medicines and Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines may interact with piperacillin and tazobactam. These include:

- medicine for gout (probenecid). This can increase the time it takes for piperacillin and tazobactam to leave your body.
- medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).
- medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.
- methotrexate (medicine used to treat cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.
- medicines that reduce the level of potassium in your blood (e.g. tablets enhancing urination or some medicines for cancer).
- medicines containing the other antibiotics tobramycin or gentamycin. Tell your doctor if you have kidney problems.

**Effect on laboratory tests**
Tell the doctor or laboratory staff that you are taking Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion if you have to provide a blood or urine sample.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will decide if Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is right for you.

Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are breast-feeding, your doctor will decide if Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is right for you.

**Driving and using machines**
The use of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion is not expected to affect the ability to drive or use machines.

**Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion contains sodium**
This medicinal product contains 4.72 mmol (108 mg) of sodium per vial of powder for solution for infusion. This should be taken into consideration if you are on a controlled sodium diet.

3. **How to use Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion**

Your doctor or other healthcare professional will give you this medicine through an infusion (a drip for 30 minutes) into one of your veins. The dose of medicine given to you depends on what you are being treated for, your age, and whether or not you have kidney problems.

**Use in adults and adolescents aged 12 years or older**
The usual dose for adults is 4 g/0.5 g piperacillin/tazobactam given every 6-8 hours, which is given into one of your veins (directly into the blood stream).

**Use in children aged 2 to 12 years**
The usual dose for children with abdominal infections is 100 mg / 12.5 mg / kg of body weight of piperacillin / tazobactam given every 8 hours into one of your veins (directly into the blood stream). The usual dose for children with low white blood cell counts is 80 mg / 10 mg / kg of body weight of piperacillin / tazobactam given every 6 hours into one of your veins (directly into the blood stream).

Your doctor will calculate the dose depending on your child’s weight but the daily dose will not exceed 4 g / 0.5 g of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion.

You will be given Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion until the sign of infection has gone completely (5 to 14 days).

**Patients with kidney problems**
Your doctor may need to reduce the dose of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion or how often you are given it. Your doctor may also want to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

**If you receive more Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion than you should**
As you will receive Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion from a doctor or other healthcare professional, you are unlikely to be given the wrong dose.
However, if you experience side effects, such as convulsions, or think you have been given too much, tell your doctor immediately.

**If you miss a dose of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion**
If you think you have not been given a dose of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion, tell your doctor or other healthcare professional immediately.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

**The serious side effects of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion are:**

- swelling of the face, lips, tongue or other parts of the body
- shortness of breath, wheezing or trouble breathing
- severe rash, itching or hives on the skin
- yellowing of the eyes or skin
- damage to blood cells (the signs include: being breathless when you do not expect it, red or brown urine, nosebleeds and bruising)

If you notice any of the above, see a doctor straight away. For frequency of these reactions, refer to the information below.

**Possible side effects are listed according to the following categories:**

- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000

**Common side effects:**

- diarrhoea, vomiting, nausea
- skin rashes

**Uncommon side effects:**

- thrush
- (abnormal) decrease in white blood cells (leukopenia, neutropenia) and platelets (thrombocytopenia)
- allergic reaction
- headache, sleeplessness
- low blood pressure, inflammation of the veins (felt as tenderness or redness in the affected area)
- jaundice (yellow staining of the skin or whites of the eyes), inflammation of the mucous lining of the mouth, constipation, indigestion, stomach upset
- increase of certain enzymes in the blood (alanine aminotransferase increased, aspartate aminotransferase increased)
- itching, nettle rash
5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

Keep this medicine out of the sight and reach of children.
For single use only. Discard any unused solution.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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

5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

Keep this medicine out of the sight and reach of children.
For single use only. Discard any unused solution.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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

Piperacillin/tazobactam is contraindicated in patients with a known allergy to penicillin. In patients sensitive to penicillin, this medication should be used with caution.

5. How to store Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

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For single use only. Discard any unused solution.
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Piperacillin/tazobactam is contraindicated in patients with a known allergy to penicillin. In patients sensitive to penicillin, this medication should be used with caution.

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

Piperacillin/tazobactam is contraindicated in patients with a known allergy to penicillin. In patients sensitive to penicillin, this medication should be used with caution.
6. Contents of the pack and other information

What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion contains

- The active substances are piperacillin and tazobactam.
  Each vial contains 2 g piperacillin (as sodium salt) and 0.25 g tazobactam (as sodium salt).
- There are no other ingredients.

What Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion looks like and the contents of the pack

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion comes in packs containing one small bottle of powder which must be dissolved into a solution before it is given to you by infusion (a slow ‘drip’) into your vein.

Packs containing 1 vial; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

Manufacturer
Laboratory Reig Jofre SA
C/ Jarma S/n Pol.Ind
45007, Toledo
Spain

This leaflet was last revised in April 2012.

The following information is intended for healthcare professionals only:

Instructions for use
Piperacillin/Tazobactam will be given by intravenous infusion (a drip for 30 minutes).

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g taclobactam)</td>
<td>10 ml</td>
</tr>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g taclobactam)</td>
<td>20 ml</td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections
- Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Sterile water for injections
- Dextran 6% in 0.9% sodium chloride

Incompatibilities
Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann's) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.
Package leaflet: Information for the user

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
Piperacillin/Tazobactam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is and what it is used for
2. What you need to know before you use Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
3. How to use Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
4. Possible side effects
5. How to store Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
6. Contents of the pack and other information

1. What Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is and what it is used for

Piperacillin belongs to the group of medicines known as “broad-spectrum penicillin antibiotics”. It can kill many kinds of bacteria. Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion can prevent some resistant bacteria from surviving the effects of piperacillin. This means that when piperacillin and tazobactam are given together, more types of bacteria are killed.

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is used in adults and adolescents to treat bacterial infections, such as those affecting the lower respiratory tract (lungs), urinary tract (kidneys and bladder), abdomen, skin or blood. Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is used in children aged 2-12 years to treat infections of the abdomen such as appendicitis, peritonitis (infection of the fluid and lining of the abdominal organs), and gallbladder (biliary) infections. Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

In certain serious infections, your doctor may consider using Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion in combination with other antibiotics.

2. What you need to know before you use Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
Do not use Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion:
- If you are allergic to piperacillin or tazobactam or any of the other ingredients of this medicine (listed in section 6)
- If you are allergic to antibiotics known as penicillins, cephalosporins or other beta-lactamase inhibitors, as you may be allergic to Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
- If you have allergies. If you have several allergies, make sure you tell your doctor or other healthcare professional before receiving this product.
- If you are suffering from diarrhoea before, or if you develop diarrhoea during or after your treatment. In this case, make sure you tell your doctor or other healthcare professional immediately. Do not take any medicine for the diarrhoea without first checking with your doctor.
- If you have low levels of potassium in your blood. Your doctor may want to check your kidneys before you take this medicine and may perform regular blood tests during treatment.
- If you have kidney or liver problems, or are receiving haemodialysis. Your doctor may want to check your kidneys before you take this medicine, and may perform regular blood tests during treatment.
- If you are taking certain medicines (called anticoagulants) to avoid an excess of blood clotting (see also Other medicines and Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion in this leaflet) or any unexpected bleeding occurs during the treatment. In this case, you should inform your doctor or other healthcare professional immediately.
- If you develop convulsions during the treatment. In this case, you should inform your doctor or other healthcare professional.

Children below 2 years
Piperacillin / tazobactam is not recommended for use in children below the age of 2 years due to insufficient data on safety and effectiveness.

Other medicines and Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines may interact with piperacillin and tazobactam.
These include:
- medicine for gout (probenecid). This can increase the time it takes for piperacillin and tazobactam to leave your body.
- medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).
- medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.
- methotrexate (medicine used to treat cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.
- medicines that reduce the level of potassium in your blood (e.g. tablets enhancing urination or some medicines for cancer).
- medicines containing the other antibiotics tobramycin or gentamycin. Tell your doctor if you have kidney problems.

Effect on laboratory tests
Tell the doctor or laboratory staff that you are taking Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion if you have to provide a blood or urine sample.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist before taking this medicine. Your doctor will decide if Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is right for you.

Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are breast-feeding, your doctor will decide if Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is right for you.

**Driving and using machines**
The use of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is not expected to affect the ability to drive or use machines.

**Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion contains sodium**
This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for infusion. This should be taken into consideration if you are on a controlled sodium diet.

3. **How to use Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion**
Your doctor or other healthcare professional will give you this medicine through an infusion (a drip for 30 minutes) into one of your veins. The dose of medicine given to you depends on what you are being treated for, your age, and whether or not you have kidney problems.

**Use in adults and adolescents aged 12 years or older**
The usual dose for adults is 4 g/0.5 g piperacillin/tazobactam given every 6-8 hours, which is given into one of your veins (directly into the blood stream).

**Use in children aged 2 to 12 years**
The usual dose for children with abdominal infections is 100 mg / 12.5 mg / kg of body weight of piperacillin / tazobactam given every 8 hours into one of your veins (directly into the blood stream). The usual dose for children with low white blood cell counts is 80 mg / 10 mg / kg of body weight of piperacillin / tazobactam given every 6 hours into one of your veins (directly into the blood stream).

Your doctor will calculate the dose depending on your child’s weight but the daily dose will not exceed 4 g / 0.5 g of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion.

You will be given Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion until the sign of infection has gone completely (5 to 14 days).

**Patients with kidney problems**
Your doctor may need to reduce the dose of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion or how often you are given it. Your doctor may also want to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

**If you receive more Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion than you should**
As you will receive Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion from a doctor or other healthcare professional, you are unlikely to be given the wrong dose. However, if you experience side effects, such as convulsions, or think you have been given too much, tell your doctor immediately.

**If you miss a dose of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion**

If you think you have not been given a dose of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion, tell your doctor or other healthcare professional immediately.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

**The serious side effects of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion are:**
- swelling of the face, lips, tongue or other parts of the body
- shortness of breath, wheezing or trouble breathing
- severe rash, itching or hives on the skin
- yellowing of the eyes or skin
- damage to blood cells (the signs include: being breathless when you do not expect it, red or brown urine, nosebleeds and bruising)

If you notice any of the above, see a doctor straight away. For frequency of these reactions, refer to the information below.

**Possible side effects are listed according to the following categories:**
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000

**Common side effects:**
- diarrhoea, vomiting, nausea
- skin rashes

**Uncommon side effects:**
- thrush
- (abnormal) decrease in white blood cells (leukopenia, neutropenia) and platelets (thrombocytopenia)
- allergic reaction
- headache, sleeplessness
- low blood pressure, inflammation of the veins (felt as tenderness or redness in the affected area)
- jaundice (yellow staining of the skin or whites of the eyes), inflammation of the mucous lining of the mouth, constipation, indigestion, stomach upset
- increase of certain enzymes in the blood (alanine aminotransferase increased, aspartate aminotransferase increased)
– itching, nettle rash
– increase of muscle metabolism product in the blood (blood creatinine increased)
– fever, injection site reaction
– yeast infection (candidal superinfection)

Rare side effects:
– (abnormal) decrease of red blood cells or blood pigment / haemoglobin, (abnormal) decrease of red blood cells due to premature breakdown (degradation) (haemolytic anaemia), small spot bruising (purpura), bleeding of the nose (epistaxis) and bleeding time prolonged, (abnormal) increase of a specific type of white blood cells (eosinophilia)
– severe allergic reaction (anaphylactic/anaphylactoid reaction, including shock)
– flushed red skin
– a certain form of infection of the colon (pseudomembranous colitis), abdominal pain
– inflammation of the liver (hepatitis), increase of a blood pigments breakdown product (bilirubin), increase of certain enzymes in the blood (blood alkaline phosphatase increased, gamma-glutamyltransferase increased)
– skin reactions with redness and formation of skin lesions (exanthema, erythema multiforme), skin reactions with blistering (bullous dermatitis)
– joint and muscle pain
– poor kidney functions and kidney problems
– rigors chill / rigidity

Very rare side effects:
– severe decrease of granular white blood cells (agranulocytosis), severe decrease of red blood cells, white blood cells and platelets (pancytopenia)
– prolonged time for blood clot formation (prolonged partial thromboplastin time, prothrombin time prolonged), abnormal lab test (positive direct Coombs), increase of platelets (thrombocythaemia)
– decrease of potassium in the blood (hypokalaemia), decrease of blood sugar (glucose), decrease of the blood protein albumin, decrease of blood total protein
– detachment of the top layer of the skin all over the body (toxic epidermal necrolysis), serious bodywide allergic reaction with skin and mucous lining rashes and various skin eruptions (Stevens-Johnson Syndrome)
– blood urea nitrogen increased

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

5. How to store Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Unopened vials: Do not store above 25°C.

For single use only. Discard any unused solution.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion contains

- The active substances are piperacillin and tazobactam.
  Each vial contains 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt).
- There are no other ingredients.

What Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion looks like and the contents of the pack

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion comes in packs containing one small bottle of powder which must be dissolved into a solution before it is given to you by infusion (a slow ‘drip’) into your vein.

Packs containing 1 vial; 50 vials (clinical package); 100 vials (clinical package).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

**Marketing authorisation holder**
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

**Manufacturer**
Laboratory Reig Jofre SA
C/ Jarra S/n Pol.Ind
45007, Toledo
Spain

This leaflet was last revised in April 2012

The following information is intended for healthcare professionals only:

**Instructions for use**
Piperacillin/Tazobactam will be given by intravenous infusion (a drip for 30 minutes).

**Intravenous use**
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved.

<table>
<thead>
<tr>
<th>Content of vial</th>
<th>Volume of solvent* to be added to vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g / 0.25 g (2 g piperacillin and 0.25 g)</td>
<td>10 ml</td>
</tr>
</tbody>
</table>
Piperacillin/Tazobactam 2/0.25 and 4/0.5g powder for solution for injection or infusion  UK/H/1010-2/001-2/DC

<table>
<thead>
<tr>
<th>Piperacillin/Tazobactam</th>
<th>20 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)</td>
<td></td>
</tr>
</tbody>
</table>

* Compatible solvents for reconstitution:
  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Sterile water for injections
  - Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

  - 0.9% (9 mg/ml) sodium chloride solution for injection
  - Glucose 5%
  - Sterile water for injections
  - Dextran 6% in 0.9% sodium chloride

**Incompatibilities**

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other substances unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer’s (Hartmann’s) solution is not compatible with piperacillin/tazobactam. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.
Piperacillin/Tazobactam 2/0.25 and 4/0.5g powder for solution for injection or infusion

LABELLING

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

Piperacillin/Tazobactam

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains: 2 g piperacillin (as sodium salt) and 0.25 g tazobactam (as sodium salt)

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

1 vial with powder for solution for infusion

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not mix or co-administer with any aminoglycoside.
Do not reconstitute or dilute with Lactated Ringer's (Hartmann's) Solution.

8. **EXPIRY DATE**

EXP
9. SPECIAL STORAGE CONDITIONS

Unopened vials: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE PRODUCTS DERIVED THEREFROM (IF APPLICABLE)

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 14894/0487

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for infusion

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### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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### 1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

Piperacillin/Tazobactam

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt)

### 3. LIST OF EXCIPIENTS

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1 vial with powder for solution for infusion

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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**Conclusion**

The proposed SmPC, PIL and labelling changes are acceptable.

**Decision – Granted 25/04/2012**