

**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**

PL 28176/0045-6

UKPAR

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**Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.50 g Powder for
Solution for Injection or Infusion
PL 28176/0045-6**

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Strides Arcolab International Limited Marketing Authorisations for the medicinal products Piperacillin/Tazobactam 2g/0.25g and 4g/0.50g powder for solution for Injection or Infusion (PL 28176/0045-6) on 24 January 2011. These medicines are only available on prescription from your doctor.

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

It may also be used to treat bacterial infections in adults and children aged 2-12 years with reduced resistance to infections due to low white blood cell counts.

In certain serious infections, your doctor may consider using Piperacillin/Tazobactam powder for solution for Injection or Infusion in combination with other antibiotics.

Piperacillin/Tazobactam powder for solution for Injection or Infusion contains two active substances called piperacillin (as piperacillin sodium) and tazobactam (as tazobactam sodium). Piperacillin belongs to the group of medicines known as 'broad spectrum penicillin antibiotics'. It can kill many kinds of bacteria. Tazobactam 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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Piperacillin/Tazobactam 2g/0.25g and 4g/0.50g powder for solution for Injection or Infusion outweigh the risks; hence Marketing Authorisations have been granted.

**Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.50 g Powder for
Solution for Injection or Infusion
PL 28176/0045-6**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Strides Arcolab International Limited Marketing Authorisations for the medicinal products Piperacillin/Tazobactam 2g/0.25g and 4g/0.50g powder for solution for Injection or Infusion (PL 28176/0045-6) on 24 January 2011. The products are prescription-only medicines (POM) used for the treatment of the following infections:

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.

Children 2 to 12 years of age

- Complicated intra-abdominal infections

Piperacillin/Tazobactam powder for solution for Injection or Infusion may also be used in the management of neutropenic patients (adults, adolescents and children aged 2 to 12 years of age) with fever suspected to be due to a bacterial infection.

Piperacillin/Tazobactam powder for solution for Injection or Infusion contains the active ingredients piperacillin (as piperacillin sodium) and tazobactam (as tazobactam sodium). Piperacillin 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. Tazobactam is a potent irreversible beta-lactamase inhibitor which protects piperacillin against enzymatic degradation from β -lactamase-producing bacteria, thus enhancing the intrinsic activity of piperacillin. The combination of piperacillin sodium and tazobactam sodium compared to piperacillin sodium 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*.

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Tazocin 2g/0.25g and 4g/0.50g Powder for Solution for Injection or Infusion (John Wyeth & Brother Limited, UK, trading as Wyeth Pharmaceuticals, UK), which were first authorised in December 1992.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of reference products that have been in clinical use for over 10 years.

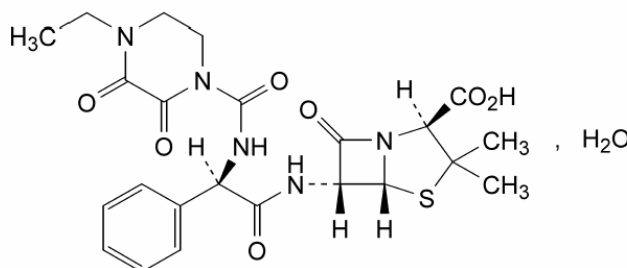
No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.50 g powder for solution for Injection or Infusion outweigh the risks; hence Marketing Authorisations have been granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE - PIPERACILLIN

INN: Piperacillin
Chemical Name: 2*S*,5*R*,6*R*)-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
Molecular Formula: C₂₃H₂₇N₅O₇S, H₂O
Structure:



Molecular weight: 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 specification limits. 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.

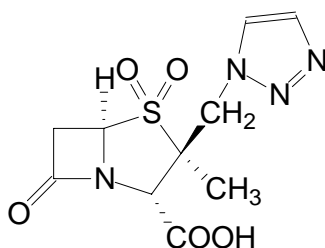
ACTIVE SUBSTANCE – TAZOBACTAM

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;
[2S-(2 α , 3 β , 5 α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azobicyclo[3,2,0]-heptane-2-carboxylic acid 4,4-dioxide.

Molecular Formula: C₁₀H₁₂N₄O₅S

Structure:



Molecular weight: 300.292 g/mol

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 the assessment of these applications tazobactam was 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 specification limits. 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 pharmaceutical excipients in these products. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Tazocin 2g/0.25g and 4g/0.50g Powder for Solution for Injection or Infusion (John Wyeth & Brother Limited, UK, trading as Wyeth Pharmaceuticals, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative impurity profiles have been provided for these products and their respective reference products, Tazocin 2g/0.25g and 4g/0.50g Powder for Solution for Injection or Infusion (John Wyeth & Brother Limited, UK, trading as Wyeth Pharmaceuticals, UK).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of all strengths 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 30ml (2g/0.25g product) and 50ml (4g/ 0.50g product) Type I glass vials with grey bromobutyl rubber stoppers and aluminium flip-off caps, with self-adhesive identification labels. Each vial is packed into a cardboard carton. The products are available in a pack size of 1 vial per carton. 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 MHRA for approval before marketing.

Satisfactory specifications and Certificates of Analysis for all packaging material have been provided. These are satisfactory. All primary packaging complies with guidelines concerning materials in contact with parenteral products.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months with the storage conditions 'Do not store above 25°C.' have been proposed for products stored in the unopened vials.

For the reconstituted solution, it is stated that unless the method of opening/reconstitution precludes the risk of microbial contamination, the Piperacillin/Tazobactam powder for solution for Injection or Infusion should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability

A bioequivalence study was not necessary to support these applications for parenteral products.

Summaries of Product Characteristics (SmPCs), Product Information Leaflets (PILs) and Labelling

The SmPCs, PILs and labelling are pharmaceutically satisfactory.

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 it contains.

MAA Forms

All aspects of the MAA forms are pharmaceutically satisfactory.

Expert Report

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

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

As the pharmacodynamic, pharmacokinetic and toxicological properties of piperacillin and tazobactam are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION

The grant of Marketing Authorisations is recommended.

CLINICAL ASSESSMENT

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.

EFFICACY

The efficacy of piperacillin and tazobactam is well-known. 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 and tazobactam, as active ingredients, have a well-established and an acceptable level of safety in the proposed indications.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PRODUCT INFORMATION LEAFLETS (PILs), LABELS

The SmPCs, PILs and labels are clinically acceptable. The SmPCs are consistent with those for the reference 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 dossier.

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.

A suitable risk management plan has been provided for these products.

CONCLUSION

The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Piperacillin/Tazobactam 2g/0.25g and 4g/0.50g powder for solution for Injection or Infusion 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. As the pharmacokinetics, pharmacodynamics and toxicology of piperacillin and tazobactam are well-known, no additional data were required.

EFFICACY

No new clinical data were submitted and none are required for these types of applications. No bioequivalence studies were submitted or required for these applications.

SAFETY

No new data were submitted and none are required for these types of applications. As the safety profile of piperacillin and tazobactam are well-known, no additional data were required.

PRODUCT LITERATURE

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along 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 reference products are interchangeable. Extensive clinical experience with piperacillin and tazobactam is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

**Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.50 g powder for solution
for Injection or Infusion
PL 28176/0045-6**

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation applications on 27 April 2006.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 14 July 2006.
- 3 Following assessment of the applications, the applications were discussed by the Chemistry, Pharmacy and Standards Expert Advisory Group (CPS-EAG) on 10 July 2007 and the Commission on Human Medicines (CHM) on 13 July 2007.
- 4 The applicant responded to the CPS-EAG's and CHM's requests of 31 July 2007, providing further information on the dossier on 28 December 2007
The applicant's response was considered by the CPS-EAG and CHM on 11 March 2008 and by the CHM on the 13 March 2008; a request for further information was sent on 26 March 2008.
The applicant responded to the CPS EAG's and CHM's requests, providing further information on the dossier on 4 June 2009.
The applicant's response was considered by the CPS-EAG on the 16 June 2009 and by the CHM on 18 June 2009; a request for further information was sent on 26 June 2009.
- 5 The applicant responded to the MHRA's requests, providing further information on the dossiers on 02 September 2009 and 23 November 2010.
- 6 The applications were determined and granted on 24 January 2011.

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 (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g

Each vial of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for Injection or Infusion contains 4.69 mmol (108 mg) of sodium.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Solution for Injection or Infusion. White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/tazobactam is indicated for the treatment of 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

Piperacillin / Tazobactam 2 g / 0.25 g Powder for Solution for Injection or Infusion may be administered by intravenous infusion (over 30 minutes)

For reconstitution instructions, see section 6.6

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 4 g/0.5 g
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
	Bacteraemia in patients with clinical signs and symptoms consistent with systemic 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):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
>40	No dose adjustment necessary
20 - 40	Maximum dose suggested: 4 g/0.5 g every 8 hours
<20	Maximum dose suggested: 4 g/0.5 g every 12 hours

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 age 12 and under by indication or condition:

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

* 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):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
> 50	No dose adjustment needed.
≤ 50	70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours.

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 aged below 2 years have not been established.

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.

4.3 Contraindications

Hypersensitivity to the Piperacillin, Tazobactam any other penicillin-antibacterial agent or to any of the excipients.

History of acute severe allergic reaction to any other beta-lactam agents (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 powder for solution for Injection or Infusion contains 4.69 mmol (108 mg) of sodium and Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion contains 9.39 mmol (216 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 Pregnancy and lactationFertility

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).

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.

Lactation

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.

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.

System Organ Class	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)
Infections and infestations		candidal superinfection		
Blood and lymphatic system disorders		leukopenia, neutropenia, thrombocytopenia	anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia	agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia
Immune system disorders		hypersensitivity	anaphylactic/anaphylactoid reaction (including shock)	
Metabolism and nutrition disorders				hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, thrombophlebitis, phlebitis	flushing	

System Organ Class	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)
Gastrointestinal disorders	diarrhoea, vomiting, nausea	jaundice, stomatitis, constipation, dyspepsia	Pseudo- membranous colitis, abdominal pain	
Hepatobiliary disorders		alanine aminotransferase increased, aspartate aminotransferase increased	hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma- glutamyltrans- ferase increased	
Skin and subcutaneous tissue disorders	rash, including maculopapular rash	urticaria, pruritus	erythema multiforme, dermatitis bullous, exanthema	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			arthralgia, 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 penicillin, including beta-lactamase inhibitors; ATC Code: J01CR05

Mechanism of action

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

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

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

Pathogen	Species-related breakpoints (S≤/R>)
Enterobacteriaceae	8/16
Pseudomonas	16/16
Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

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

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

Susceptibility

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

Groupings of relevant species according to piperacillin/tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> <i>Listeria monocytogenes</i> <i>Staphylococcus aureus</i> , methicillin-susceptible ^f <i>Staphylococcus</i> species, <i>coagulase negative</i> , methicillin-susceptible <i>Streptococcus pyogenes</i> <i>Group B streptococci</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Citrobacter koseri</i> <i>Haemophilus influenza</i> <i>Moraxella catarrhalis</i> <i>Proteus mirabilis</i>
<u>Anaerobic Gram-positive micro-organisms</u> <i>Clostridium</i> species <i>Eubacterium</i> species <i>Peptostreptococcus</i> species
<u>Anaerobic Gram-negative micro-organisms</u> <i>Bacteroides fragilis</i> group <i>Fusobacterium</i> species <i>Porphyromonas</i> species <i>Prevotella</i> species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecium</i> ^{§,+} <i>Streptococcus pneumonia</i> <i>Streptococcus viridans</i> group
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> [§] <i>Burkholderia cepacia</i> <i>Citrobacter freundii</i> <i>Enterobacter</i> species <i>Escherichia coli</i> <i>Klebsiella pneumonia</i> <i>Morganella morganii</i> <i>Proteus vulgaris</i> <i>Providencia</i> ssp. <i>Pseudomonas aeruginosa</i>
<i>Serratia</i> species
INHERENTLY RESISTANT ORGANISMS
<u>Aerobic Gram-positive micro-organisms</u> <i>Corynebacterium jeikeium</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Legionella</i> species <i>Stenotrophomonas maltophilia</i> ^{+,§}
<u>Other microorganisms</u>
<i>Chlamydia pneumonia</i>
<i>Mycoplasma pneumonia</i>
§ 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.

Metabolism

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

Elimination

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

Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the administered dose appearing as unchanged substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of piperacillin/tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

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

Special populations

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

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

Haemodialysis removes 30% to 50% of piperacillin/tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.

Paediatric population

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

Elderly patients

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

Race

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

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 F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin/tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin/tazobactam in the rat.

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 substance 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.

Due to chemical instability, Piperacillin/Tazobactam should not be used with solutions containing only 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: 24 months

Reconstituted solution in vial

Chemical and physical in-use stability has been demonstrated for 12 hours when stored at 25°C and 48 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 12 hours at 25°C and for 48 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, unless the method of opening/reconstitution precludes the risk of microbial contamination, the Piperacillin/Tazobactam Powder for Solution for Injection or Infusion 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 25°C and for 48 hours at 2°C to 8°C, unless reconstitution has 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 of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vials with dark grey rubber plug and aluminium seal. Each vial is packed in a carton.

Pack sizes: 1 vials per carton

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. (for details on handling, please see below)

Content of vial	Volume of solvent* to be added to vial
Piperacillin/Tazobactam 2 g/0.25 g Powder for solution for Injection or Infusion	10 mL

* Compatible solvents for reconstitution:

- 0.9 % (9 mg/mL) sodium chloride solution for injection
- Sterile water for injections⁽¹⁾
- Glucose 5 %

⁽¹⁾ Maximum recommended volume of sterile water for injection per dose is 50 mL

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
- Sterile water for injections
- Glucose 5 %
- Dextran 6% in 0.9 % sodium chloride

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
STRIDES ARCOLAB INTERNATIONAL LIMITED**

Unit 4, Metro Centre,
Tolpits Lane,
Watford, Hertfordshire
WD 189 SS UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 28176/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/01/2011

10 DATE OF REVISION OF THE TEXT

24/01/2011

1 NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 4 g/0.50 g powder for solution for Injection or 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 of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for Injection or Infusion contains 9.39 mmol (216 mg) of sodium.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Solution for Injection or Infusion. White to off-white powder.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Piperacillin/tazobactam is indicated for the treatment of 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

Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion may be administered by intravenous infusion (over 30 minutes).

For reconstitution instructions, see section 6.6.

Posology

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

Adult and adolescent patientsInfections

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 4 g/0.5 g
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
	Bacteraemia in patients with clinical signs and symptoms consistent with systemic 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):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
> 40	No dose adjustment necessary
20 - 40	Maximum dose suggested: 4 g/0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g/0.5 g every 12 hours

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 age 12 and under by indication or condition:

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

* 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):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
> 50	No dose adjustment needed.
≤ 50	70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours.

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 aged below 2 years have not been established.

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.

4.3 Contraindications

Hypersensitivity to the Piperacillin, Tazobactam any other penicillin-antibacterial agent or to any of the excipients.

History of acute severe allergic reaction to any other beta-lactam agents (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 2g /0.25 g Powder for Solution for Injection or Infusion contains 4.69 mmol (108 mg) of sodium and Piperacillin / Tazobactam 4 g 0.5 g Powder for Solution for Injection or Infusion contains 9.39 mmol (216 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 Pregnancy and lactation

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).

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.

Lactation

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.

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.

System Organ Class	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)
Infections and infestations		candidal superinfection		
Blood and lymphatic system disorders		leukopenia, neutropenia, thrombocytopenia	anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia	agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia
Immune system disorders		hypersensitivity	anaphylactic/ anaphylactoid reaction (including shock)	
Metabolism and nutrition disorders				hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, thrombophlebitis, phlebitis	flushing	
Gastrointestinal disorders	diarrhoea, vomiting, nausea	jaundice, stomatitis, constipation, dyspepsia	Pseudo-membranous colitis, abdominal pain	
Hepatobiliary disorders		alanine aminotransferase increased, aspartate	hepatitis, blood bilirubin increased, blood alkaline	

System Organ Class	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)
		aminotransferase increased	phosphatase increased, gamma-glutamyltrans-ferase increased	
Skin and subcutaneous tissue disorders	rash, including maculopapular rash	urticaria, pruritus	erythema multiforme, dermatitis bullous, exanthema	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			arthralgia, 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 penicillin, including beta-lactamase inhibitors; ATC Code: J01CR05

Mechanism of action

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

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

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

Pathogen	Species-related breakpoints (S≤/R>)
Enterobacteriaceae	8/16
Pseudomonas	16/16
Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

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

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

Susceptibility

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

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

<i>Streptococcus viridans group</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> § <i>Burkholderia cepacia</i> <i>Citrobacter freundii</i> <i>Enterobacter species</i> <i>Escherichia coli</i> <i>Klebsiella pneumonia</i> <i>Morganella morganii</i> <i>Proteus vulgaris</i> <i>Providencia ssp.</i> <i>Pseudomonas aeruginosa</i>
<i>Serratia species</i>
INHERENTLY RESISTANT ORGANISMS
<u>Aerobic Gram-positive micro-organisms</u> <i>Corynebacterium jeikeium</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Legionella species</i> <i>Stenotrophomonas maltophilia</i> ^{+,§}
<u>Other microorganisms</u>
<i>Chlamydia pneumonia</i>
<i>Mycoplasma pneumonia</i>
§ 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.

Metabolism

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

Elimination

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

Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the administered dose appearing as unchanged substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of piperacillin / tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by

dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

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

Special populations

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

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

Haemodialysis removes 30% to 50% of piperacillin / tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.

Paediatric population

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

Elderly patients

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

Race

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

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 F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin/tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin tazobactam in the rat.

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 substance 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 substance in a syringe or infusion bottle since compatibility has not been established

Due to chemical instability, Piperacillin/Tazobactam should not be used with solutions containing only 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: 24 months

Reconstituted solution in vial

Chemical and physical in-use stability has been demonstrated for 12 hours when stored at 25°C and 48 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 12 hours at 25°C and for 48 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, unless the method of opening/reconstitution precludes the risk of microbial contamination, the Piperacillin/Tazobactam powder for solution for Injection or Infusion 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 25°C and for 48 hours at 2°C to 8°C, unless reconstitution has 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 of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vials with dark grey rubber plug and aluminium seal. Each vial is packed in a carton.

Pack sizes: 1 vials per carton

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. (for details on handling, please see below)

Content of vial	Volume of solvent* to be added to vial
Piperacillin/Tazobactam 4 g/0.5 g Powder for solution for Injection or Infusion	20 mL

* Compatible solvents for reconstitution:

- 0.9 % (9 mg/mL) sodium chloride solution for injection
- Sterile water for injections⁽¹⁾
- Glucose 5 %

⁽¹⁾ Maximum recommended volume of sterile water for injection per dose is 50 mL

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
- Sterile water for injections
- Glucose 5 %
- Dextran 6% in 0.9 % sodium chloride

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**
STRIDES ARCOLAB INTERNATIONAL LIMITED
Unit 4, Metro Centre,
Tolpits Lane,
Watford, Hertfordshire
WD 189 SS
UNITED KINGDOM
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 28176/0046
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
24/01/2011
- 10 DATE OF REVISION OF THE TEXT**
24/01/2011

MODULE 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

PIPERACILLIN/TAZOBACTAM 2 g/0.25 g POWDER FOR SOLUTION FOR INJECTION OR INFUSION [Piperacillin / Tazobactam]

Read all of this leaflet carefully before you start taking 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 penicillin antibiotics'. It can kill many kinds of bacteria. Tazobactam 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 Injection or 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 Injection or 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 Injection or Infusion is used in children aged 2-12 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 Injection or 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 Injection or Infusion in combination with other antibiotics.

2. BEFORE YOU USE 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 any of the other ingredients of Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion
- If you are allergic (hypersensitive) 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 Injection or Infusion

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 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 diarrhoea medicine 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 **Using other medicines** 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.

Using other medicines

Please tell your doctor or other healthcare professional 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.

- 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 lab tests

Tell the doctor or laboratory staff that you are taking Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion if you have to provide a blood or urine sample.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are trying to become pregnant, tell your doctor or other healthcare professional before receiving this product. Your doctor will decide if Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or 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 Injection or Infusion is right for you.

Driving and using machines

The use of Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion is not expected to affect the ability to drive or use machines.

Important information about some of the ingredients of Piperacillin/Tazobactam 2 g/0.25 g powder for solution for Injection or Infusion

Piperacillin/Tazobactam 2 g/0.25 g powder for solution for Injection or Infusion contains 4.69 mEq (108 mg) of sodium.

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 INJECTION OR 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

Adults and adolescents aged 12 years or older

The usual dose is 4 g / 0.5 g of piperacillin / tazobactam given every 6-8 hours, which is given into one of your veins (directly into the blood stream).

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 Powder for Solution for Injection or Infusion.

You will be given Piperacillin/Tazobactam Powder for Solution for Injection or 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 Powder for Solution for Injection or 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 are given more Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion than you should

As you will receive Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion by a doctor or other healthcare professional, you are unlikely to be given the wrong dose. However, if you experience bad 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 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 or other healthcare professional immediately.

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

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or other healthcare professional:

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 2 g/0.25 g POWDER FOR SOLUTION FOR INJECTION OR INFUSION

Keep out of the reach and sight of children.

Do not use Piperacillin/Tazobactam Powder for Solution for Injection or Infusion 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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or 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)

What Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion looks like and contents of the pack

Piperacillin and Tazobactam 2 g/0.25g Powder for Solution for Injection or Infusion

White to off white powder filled in flint vials with rubber plug and aluminium seal. Each vial is packed in a carton.

Pack sizes: 1 vials per carton

Marketing Authorisation Holder

Strides Arcolab International Limited
Unit 4, Metro Centre,
Tolpits Lane, Watford, Hertfordshire
WD 189 SS UNITED KINGDOM
Telephone: 044 1923 255580
Email: peter@co-pharma.co.uk

Site Responsible for Batch Release in the EEA

Strides Arcolab Polska Sp z o o
10, Daniszewska Str
03-230 Warsaw, Poland
Ph: 0048 22 6140081

This medicinal product is authorised in the Member States of the EEA under the following names:>

Not applicable

This leaflet was last approved in {MM/YYYY}.

Not applicable

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 The following information is intended for medical or healthcare professionals only:

Piperacillin/Tazobactam 2 g/0.25 g Powder for solution for Injection or Infusion

Instructions for Use.

Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion 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 (details for handling, please see below).

Content of vial	Volume of solvent* to be added to vial
2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)	10 ml

*Compatible solvents for reconstitution:

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injection⁽¹⁾
- Glucose 5%

⁽¹⁾ Maximum recommended volume of sterile water for injection per dose is 50 ml.

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 injection
- Dextran 6% in 0.9% sodium chloride

For slow intravenous injection and slow intravenous infusion incompatibilities with diluents and other medicinal products.

- Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion.
- When used concurrently with another antibiotic (e.g. aminoglycosides), Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion must be administered separately. Mixing with an aminoglycoside *in-vitro* can cause inactivation of the aminoglycoside.
- Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.
- Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion should be administered through an infusion set separately from any other drugs unless compatibility is proven.
- Due to chemical instability, Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion should not be used in solutions that contain sodium bicarbonate.
- Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Injection or Infusion should not be added to blood products or albumin hydrolysates.

SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product should not be stored above 25°C

After reconstitution, chemical and in-use stability has been demonstrated for 12 hours when stored at 25°C and 48 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the Piperacillin/Tazobactam Powder for Solution for Injection 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 25°C and for 48 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated.

PACKAGE LEAFLET: INFORMATION FOR THE USER**PIPERACILLIN/TAZOBACTAM 4 g/0.5 g
POWDER FOR SOLUTION FOR INJECTION or INFUSION
(Piperacillin / Tazobactam)**

Read all of this leaflet carefully before you start taking 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 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 4 g/0.5 g Powder for Solution for Injection or Infusion
3. How Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion is given
4. Possible side effects
5. How to store Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion
6. Further information

1. WHAT PIPERACILLIN/TAZOBACTAM 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 penicillin antibiotics'. It can kill many kinds of bacteria. Tazobactam 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 Injection or 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 Injection or 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 Injection or Infusion is used in children aged 2-12 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 Injection or 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 Injection or Infusion in combination with other antibiotics.

2. BEFORE YOU USE PIPERACILLIN/TAZOBACTAM 4 g/0.5 g POWDER FOR SOLUTION FOR INJECTION OR INFUSION

Do not use Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion

- If you are allergic (hypersensitive) to piperacillin or tazobactam, or any of the other ingredients of Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion
- If you are allergic (hypersensitive) 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 Injection or Infusion

Take special care with Piperacillin/Tazobactam 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 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 diarrhoea medicine 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 **Using other medicines** 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.

Using other medicines

Please tell your doctor or other healthcare professional 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.

- 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 lab tests

Tell the doctor or laboratory staff that you are taking Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion if you have to provide a blood or urine sample.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are trying to become pregnant, tell your doctor or other healthcare professional before receiving this product. Your doctor will decide if Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or 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 Injection or Infusion is right for you.

Driving and using machines

The use of Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion is not expected to affect the ability to drive or use machines.

Important information about some of the ingredients of Piperacillin/Tazobactam 4 g/0.5 g powder for solution for Injection or Infusion

Piperacillin/Tazobactam 4 g/0.5 g powder for solution for Injection or Infusion contains 9.39 mEq (216 mg) of sodium.

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 INJECTION OR 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

Adults and adolescents aged 12 years or older

The usual dose is 4 g / 0.5 g of piperacillin / tazobactam given every 6-8 hours, which is given into one of your veins (directly into the blood stream).

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 Powder for Solution for Injection or Infusion.

You will be given Piperacillin/Tazobactam Powder for Solution for Injection or 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 Powder for Solution for Injection or 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 are given more Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion than you should

As you will receive Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion by a doctor or other healthcare professional, you are unlikely to be given the wrong dose. However, if you experience bad 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 Injection or Infusion

If you think you have not been given a dose of Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion, tell your doctor or other healthcare professional immediately.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion can cause side effects, although not everybody gets them.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or other healthcare professional:

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 INJECTION OR INFUSION

Keep out of the reach and sight of children.

Do not use Piperacillin/Tazobactam Powder for Solution for Injection or Infusion 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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or 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)

What Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion looks like and contents of the pack

Piperacillin and Tazobactam 4 g/0.5g Powder for Solution for Injection or Infusion

White to off white powder filled in flint vials with rubber plug and aluminium seal. Each vial is packed in a carton.

Pack sizes: 1 vials per carton

Marketing Authorisation Holder

Strides Arcolab International Limited
Unit 4, Metro Centre,
Tolpits Lane, Watford, Hertfordshire
WD 189 SS UNITED KINGDOM
Telephone: 044 1923 255580
Email: peter@co-pharma.co.uk

Site Responsible for Batch Release in the EEA

Strides Arcolab Polska Sp z o o
10, Daniszewska Str
03-230 Warsaw, Poland
Ph: 0048 22 6140081

This medicinal product is authorised in the Member States of the EEA under the following names:>

Not applicable

This leaflet was last approved in {MM/YYYY}.

Not applicable

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 The following information is intended for medical or healthcare professionals only:

Piperacillin/Tazobactam 4 g/0.5 g Powder for solution for Injection or Infusion

Instructions for Use.

Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion 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 (details for handling, please see below).

Content of vial	Volume of solvent* to be added to vial
4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)	20 ml

***Compatible solvents for reconstitution:**

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injection⁽¹⁾
- Glucose 5%
- ⁽¹⁾ Maximum recommended volume of sterile water for injection per dose is 50 ml.

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 injection
- Dextran 6% in 0.9% sodium chloride

For slow Intravenous Injection and slow Intravenous Infusion Incompatibilities with diluents and other medicinal products.

- Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion.
- When used concurrently with another antibiotic (e.g. aminoglycosides), Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion must be administered separately. Mixing with an aminoglycoside *in-vitro* can cause inactivation of the aminoglycoside.
- Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.
- Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion should be administered through an infusion set separately from any other drugs unless compatibility is proven.
- Due to chemical instability, Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion should not be used in solutions that contain sodium bicarbonate.
- Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Injection or Infusion should not be added to blood products or albumin hydrolysates.

SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product should not be stored above 25°C

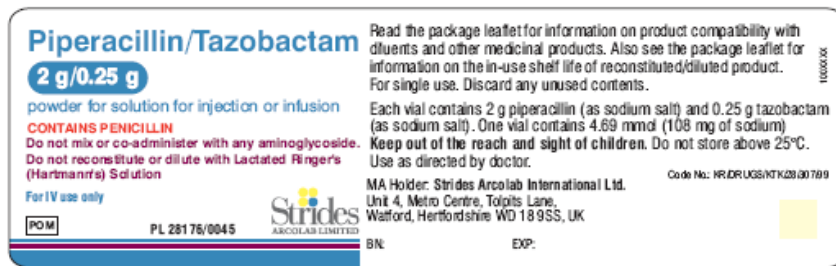
After reconstitution, chemical and in-use stability has been demonstrated for 12 hours when stored at 25°C and 48 hours when stored in a refrigerator at 2-8°C.

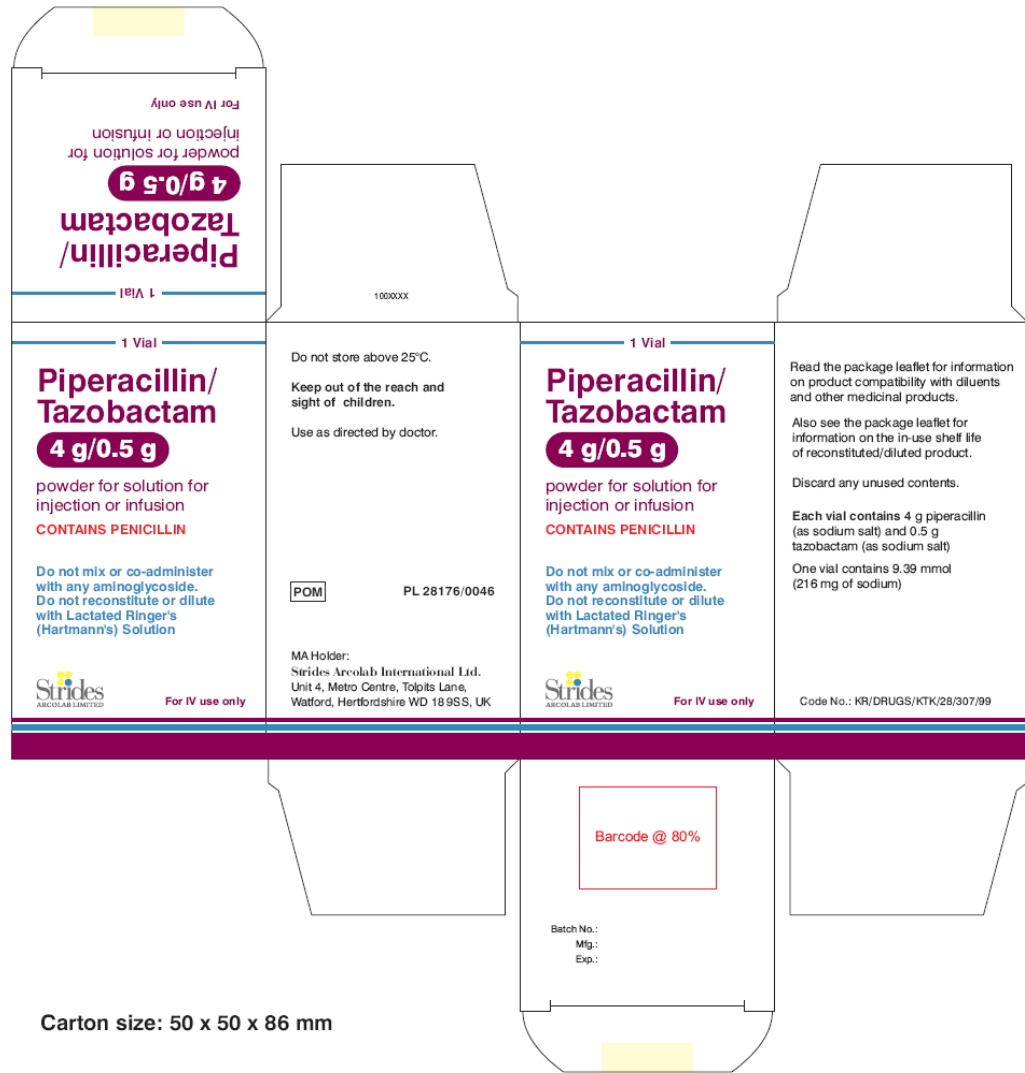
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the Piperacillin/Tazobactam Powder for Solution for Injection should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 25°C and for 48 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated.

LABELLING



Carton size: 45 x 45 x 70 mm





Carton size: 50 x 50 x 86 mm

