PACKAGE LEAFLET

Package leaflet: Information for the user

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

Piperacillin/tazobactam 4 g/0.5 g powder for solution for infusion

piperacillin/tazobactam

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Piperacillin/tazobactam is and what it is used for
2. What you need to know before you use Piperacillin/tazobactam
3. How to use Piperacillin/tazobactam
4. Possible side effects
5. How to store Piperacillin/tazobactam
6. Contents of the pack and other information

1. What Piperacillin/tazobactam 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 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 may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

Piperacillin/tazobactam is used in children aged 2-12 years to treat infections of the abdomen such as appendicitis, peritonitis (infection of the fluid and lining of the abdominal organs), and gallbladder (biliary) infections. Piperacillin/tazobactam 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 in combination with other antibiotics.

2. What you need to know before you use Piperacillin/tazobactam

Do not use Piperacillin/tazobactam :

- if you are allergic to piperacillin or tazobactam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to antibiotics known as penicillins, cephalosporins or other beta-lactamase inhibitors, as you may be allergic to piperacillin/tazobactam.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Piperacillin/tazobactam.

- if you have allergies. If you have several allergies, make sure you tell your doctor or other healthcare professional before receiving this product.

- if you are suffering from diarrhoea before, or if you develop diarrhoea during or after your treatment. In this case, make sure you tell your doctor or other healthcare professional immediately. Do not take any medicine for the diarrhoea without first checking with your doctor.

- if you have low levels of potassium in your blood. Your doctor may want to check your kidneys before you take this medicine and may perform regular blood tests during treatment.

- if you have kidney or liver problems, or are receiving haemodialysis. Your doctor may want to check your kidneys before you take this medicine, and may perform regular blood tests during treatment.

- if you are taking certain medicines (called anticoagulants) to avoid an excess of blood clotting (see also **Other medicines and Piperacillin/tazobactam** 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 fits (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.

Haemophagocytic lymphohistiocytosis

There have been reports about a disease in which the immune system makes too many of otherwise normal white blood cells called histiocytes and lymphocytes, resulting in inflammation (haemophagocytic lymphohistiocytosis). This condition may be life-threatening if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, feeling weak, feeling lightheaded, shortness of breath, bruising, or skin rash, contact your doctor immediately.

Children

The use of piperacillin / tazobactam is not recommended for use in children below the age of 2 years due to insufficient data on safety and effectiveness.

Other medicines and Piperacillin/tazobactam

Tell your doctor or other healthcare professional if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Some medicines may interact with piperacillin and tazobactam.

These include:

- medicine for gout (probenecid). This can increase the time it takes for piperacillin and tazobactam to leave your body.

- medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).

- medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.

- methotrexate (medicine used to treat cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.

- medicines that reduce the level of potassium in your blood (e.g. tablets enhancing urination or some medicines for cancer).

- medicines containing the other antibiotics tobramycin, gentamicin or vancomycin. Tell your doctor if you have kidney problems.

Effect on laboratory tests

Tell the doctor or laboratory staff that you are taking piperacillin/tazobactam if you have to provide a blood or urine sample.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or other healthcare professional for advice before receiving this medicine. Your doctor will decide if piperacillin/tazobactam 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 is right for you.

Driving and using machines

The use of piperacillin/tazobactam is not expected to affect the ability to drive or use machines.

Piperacillin/tazobactam contains sodium

Piperacillin/tazobactam 2 g / 0.25 g

This medicine contains 103.25 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 5.13% of the recommended maximum daily dietary intake of sodium for an adult.

Piperacillin/tazobactam 4 g / 0.5 g

This medicine contains 206.48 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 10.32% of the recommended maximum daily dietary intake of sodium for an adult.

This should be taken into consideration if you are on a controlled-sodium diet.

3. How to use Piperacillin/tazobactam

Your doctor or other healthcare professional will give you this medicine through an infusion (a drip for 30 minutes) into one of your veins.

Dosage

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 above 12 years of age

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 each individual dose will not exceed 4 g / 0.5 g of piperacillin/tazobactam.

You will be given piperacillin/tazobactam 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 or how often you are given it. Your doctor may also want to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

If you receive more Piperacillin/tazobactam than you should

As you will receive Piperacillin/tazobactam from a doctor or other healthcare professional, you are unlikely to be given the wrong dose. However, if you experience side effects, such as convulsions, or think you have been given too much, tell your doctor immediately.

If you miss a dose of Piperacillin/tazobactam

If you think you have not been given a dose of Piperacillin/tazobactam, tell your doctor or other healthcare professional immediately.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
See a doctor immediately if you experience any of these potentially serious side effects of piperacillin/tazobactam:

<u>The serious side effects (with frequency in brackets) of piperacillin/tazobactam are:</u>

- serious skin rashes [Stevens-Johnson syndrome, dermatitis bullous (Not known), dermatitis exfoliative (Not known), toxic epidermal necrolysis (Rare)] appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs include ulcers in the mouth, throat, nose, extremities, genitals and conjunctivitis (red and swollen eyes). The rash may progress to widespread blistering or peeling of the skin and potentially may be life-threatening.
- severe potentially fatal allergic condition (drug reaction with eosinophilia and systemic symptoms) that can involve the skin and most importantly other organs under the skin such as the kidney and the liver.

- a skin condition (acute generalised exanthematous pustulosis) accompanied by fever, which consists of numerous tiny fluid filled blisters contained within large areas of swollen and reddened skin.
- swelling of the face, lips, tongue or other parts of the body (Not known)
- shortness of breath, wheezing or trouble breathing (Not known)
- severe rash or hives (Uncommon), itching or rash on the skin (Common)
- yellowing of the eyes or skin (Not known)
- damage to blood cells [the signs include: being breathless when you do not expect it, red or brown urine (Not known), nosebleeds (Rare) and small spot bruising (Not known)], severe decrease in white blood cells (Rare)
- severe or persistent diarrhoea accompanied by a fever or weakness (Rare)

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

Very common side effects (may affect more than 1 in 10 people)**:**
- diarrhoea

Common side effects (may affect up to 1 in 10 people)**:**
- yeast infection
- decrease in platelets, decrease of red blood cells or blood pigment / haemoglobin, abnormal lab test (positive direct Coombs), prolonged blood clotting time (activated partial thromboplastin time prolonged)
- decrease in blood protein
- headache, sleeplessness
- abdominal pain, vomiting, nausea, constipation, upset stomach
- increase in blood liver enzymes
- skin rash, itching
- abnormal kidney blood tests
- fever, injection site reaction

Uncommon side effects (may affect up to 1 in 100 people)**:**
- decrease in white blood cells (leukopenia), prolonged blood clotting time (prothrombin time prolonged)
- decreased blood potassium, decreased blood sugar
- fits (convulsions), seen in patients on high doses or with kidney problems
- low blood pressure, inflammation of the veins (felt as tenderness or redness in the affected area), reddening of skin
- increase of a blood pigment breakdown product (bilirubin)
- skin reactions with redness, formation of skin lesions, nettle rash
- joint and muscle pain
- chills

Rare side effects (may affect up to 1 in 1,000 people):
- severe decrease in white blood cells (agranulocytosis), bleeding of the nose
- serious infection of the colon, inflammation of the mucous lining of the mouth
- detachment of the top layer of the skin all over the body (toxic epidermal necrolysis)

Not known side effects (frequency cannot be estimated from the available data):

- severe decrease of red blood cells, white blood cells and platelets (pancytopenia), decrease in white blood cells (neutropenia), decrease of red blood cells due to premature breakdown or degradation, small spot bruising, bleeding time prolonged, increase of platelets, increase of a specific type of white blood cells (eosinophilia)
- allergic reaction and severe allergic reaction
- inflammation of the liver, yellow staining of the skin or whites of the eyes
- serious body wide allergic reaction with skin and mucous lining rashes, blistering and various skin eruptions (Stevens-Johnson Syndrome), severe allergic condition involving skin and other organs such as the kidney and the liver (drug reaction with eosinophilia and systemic symptoms), numerous tiny fluid filled blisters contained within large areas of swollen and reddened skin accompanied by fever (acute generalised exanthematous pustulosis), skin reactions with blistering (dermatitis bullous)
- poor kidney functions and kidney problems
- a form of lung disease where eosinophils (a form of white blood cell) appear in the lung in increased numbers.
- acute disorientation and confusion (delirium).

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

Beta-lactam antibiotics, including piperacillin tazobactam, may lead to manifestations of encephalopathy and convulsions.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Piperacillin/tazobactam

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and the carton after EXP. The expiry date refers to the last day of that month.

Unopened vials: This medicinal product does not require any special storage conditions.

For single use only. Discard any unused solution.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicine you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Piperacillin/tazobactam contains

Piperacillin/tazobactam 2 g / 0.25 g

- The active substances are piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.
- There are no other ingredients.

Piperacillin/tazobactam 4 g / 0.5 g

- The active substances are piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.
- There are no other ingredients.

What Piperacillin/tazobactam looks like and contents of the pack

Piperacillin/tazobactam 2 g/0.25 g is off-white to white cake or powder for solution for infusion

Available in 30ml Type I glass Vial, butyl rubber stoppers and aluminium plastic combined cap.

Pack sizes: 1, 5, 10, 12, 25 or 50 vials per carton.

Piperacillin/tazobactam 4 g/0.5 g is off-white to white cake or powder for solution for infusion

Available in 50ml Type I glass Vial, butyl rubber stoppers and aluminium plastic combined cap.

Pack sizes: 1, 5, 10, 12, 25 or 50 vials per carton.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Tillomed Laboratories Limited,
220 Butterfield, Great Marlings,
Luton, LU2 8DL,
United Kingdom

Manufacturer[1]

1) **Tillomed Laboratories Ltd.**
   220 Butterfield, Great Marlings,
   Luton, LU2 8DL
   United Kingdom

2) **Kymos, S.L.**
   Ronda de Can Fatjó,
   7B (Parque Tecnológico del Vallès),
   Cerdanyola del Vallès,
   08290, Barcelona,
   Spain

3) **Pharmadox Healthcare Ltd.**
   KW20A Kordin Industrial Park,
   Paola PLA 3000, Malta

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The following information is intended for healthcare professionals only:

Note: Use for bacteraemia due to extended-beta-lactamase (ESBL) producing E. coli and K. pneumoniae (ceftriaxone non-susceptible), is not recommended in adult patients.

How to store
Unopened vials: This medicinal product does not require any special storage conditions.

Reconstituted solution in vial
Chemical and physical in-use stability has been demonstrated for up to 48 hours when stored in a refrigerator at 2-8°C and for 12 hours when stored below 25°C, when reconstituted with one of the compatible solvents for reconstitution (see Instructions for use below).

Diluted reconstituted solution, for infusion
The diluted reconstituted solution when using one of the compatible solvents at the suggested dilution volume (see Instructions for use below), demonstrated chemical and physical in-use stability for up to 48 hours when stored in a refrigerator at 2-8°C and for 12 hours when stored below 25°C.

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 2-8°C or 12 hours when stored below 25°C.

Instructions for use
Piperacillin/tazobactam will be given by intravenous infusion (a drip for 30 minutes).

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes (for details on 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
4 g / 0.50 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 injections[(1)]
- Dextrose 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
- Dextrose 5%

- Dextran 6% in 0.9% (9 mg/ml) sodium chloride

Incompatibilities

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with aminoglycosides, *in vitro*, can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible with piperaciliin/tazobactam *in vitro* in certain diluents at specific concentrations (see **Co-administration of Piperacillin/tazobactam with aminoglycosides** below).

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

Because of chemical instability, piperacillin/tazobactam should not be used with solutions containing only sodium bicarbonate.

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

Co-administration of Piperacillin/tazobactam with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

In circumstances where co-administration is recommended, piperacillin/tazobactam is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	**Piperacillin/tazobactam Dose**	**Piperacillin/tazobactam Diluent volume (ml)**	**Aminoglycoside concentration range* (mg/ml)**	**Acceptable diluents**
Amikacin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

* The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening) and renal function (creatinine clearance).

Compatibility of piperacillin/tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dose of piperacillin/tazobactam listed in the above table have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site in any manner other than listed above may result in inactivation of the aminoglycoside by piperacillin/tazobactam.