Package leaflet: Information for the user
Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion
Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion
Piperacillin (as Sodium) with Tazobactam (as Sodium)

Please read all of this leaflet carefully before you start taking 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 is 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.

The name of your medicine is Piperacillin/Tazobactam 2g/0.25g and 4g/0.5g Powder for Solution for Infusion.
In the rest of this leaflet Piperacillin/Tazobactam 2g/0.25g and 4g/0.5g Powder for Solution for Infusion is called Piperacillin with Tazobactam.

What is in this leaflet:

1. What Piperacillin with Tazobactam is and what it is used for

Piperacillin belongs to the group of medicines called 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 with 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 with Tazobactam may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).
Piperacillin with 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 with 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 with Tazobactam in combination with other antibiotics.

2. What you need to know before you are given Piperacillin with Tazobactam

Do not use Piperacillin with Tazobactam:
- if you are allergic to piperacillin or tazobactam or any of the other ingredients of this medicine
- if you are allergic to antibiotics known as penicillins, cephalosporins or other beta-lactamase inhibitors, as you may be allergic to Piperacillin with Tazobactam.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Piperacillin with 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 liver or kidney 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.

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 below 2 years
Piperacillin with 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 with Tazobactam
Please tell your doctor or other healthcare professional if you are taking, 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 tor 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 totobramycin or gentamycin. Tell your doctor if you have kidney problems.

Effect on laboratory tests
Tell the doctor or laboratory staff that you are taking Piperacillin with Tazobactam 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 this medicine 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 whether this medicine is right for you.
Your doctor will advise you if you should have this medicine.

Driving and using machines
The use of Piperacillin with Tazobactam is not expected to affect the ability to drive or use machines.

Piperacillin with Tazobactam contains sodium
Piperacillin/Tazobactam 2g/0.25g contains 4.72mmol (109mg) of sodium per vial of powder for solution for infusion. *Piperacillin/Tazobactam* 4g/0.5g contains 9.44mmol (217mg) of sodium per vial of powder for solution for infusion.
To be taken into consideration by patients on a controlled sodium diet.

3. How Piperacillin with Tazobactam is given

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.

This product must not be mixed or Co-administered with any aminoglycoside and must not be reconstituted or diluted with Lactated Ringer's (Hartmann's) solution.

Adults and adolescents aged 12 years or older
The recommended dose is 4g/0.5g piperacillin/tazobactam given every 6 to 8 hours, which is given into one of your veins (directly into the blood stream).

Children aged 2 to 12 years
The recommended dose for children with abdominal infections is 100mg/12.5mg/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 80mg/10mg/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 4g/0.5g.
You will be given Piperacillin with 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 with Tazobactam or how often you are given it. Your doctor may also

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INFORMATION FOR HEALTHCARE PROFESSIONALS
Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion.
Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion.
Please refer to the Summary of Product Characteristics (SmPC) for further details on this product.

Qualitative and Quantitative Composition
Piperacillin/Tazobactam 2g/0.25g:
Each vial contains 2g piperacillin (as sodium salt) and 0.25g tazobactam (as sodium salt).
One vial of powder for solution for infusion contains 4.72mmol (109mg) of sodium.
Piperacillin/Tazobactam 4g/0.5g:
Each vial contains 4g piperacillin (as sodium salt) and 0.5g tazobactam (as sodium salt).

One vial of powder for solution for infusion contains 9.44mmol (217mg) of sodium.

For a full list of excipients see section 6.1.

Pharmaceutical Form
Powder for solution for infusion.
White to off white powder.

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

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

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

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

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology and method of administration
Posology
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.
Adult and adolescent patients
Infections
The usual dose is 4g piperacillin / 0.5g tazobactam given every eight hours.
For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4g piperacillin / 0.5g tazobactam administered every six 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 4g / 0.5g
Every six hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every eight 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 (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: 4g / 0.5g every eight hours
< 20	Maximum dose suggested: 4g / 0.5g every 12 hours

For patients on haemodialysis, one additional dose of Piperacillin/Tazobactam 2g/0.25g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in four 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 40ml/min.
Paediatric population (2-12 years of age)
Infections
The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

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

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

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 with Tazobactam than you should

As you will be given Piperacillin with Tazobactam by 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 with Tazobactam

If you think you have not been given a dose of Piperacillin with 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 other health care professional.

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 with this medicine:

The serious side effects (with frequency in brackets) of this medicine are:

- 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: 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 signs of altered brain function (encephalopathy) and convulsions.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for the 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 with Tazobactam

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

Do not use your medicine after the expiry date which is stated on the carton and the label on the small glass container (vial). The expiry date refers to the last day of that month.

Do not store above 25°C.

Made-up solutions may be stored for up to 24 hours in a refrigerator (2°C - 8°C). For single use only. Discard any unused solution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What Piperacillin with Tazobactam contains

The active substances are piperacillin as the sodium salt and tazobactam as the sodium salt. There are no other ingredients.

Piperacillin with Tazobactam 2g/0.25g contains 2g of piperacillin (as sodium salt) and 0.25g of tazobactam (as sodium salt).

Piperacillin with Tazobactam 4g/0.5g contains 4g of piperacillin (as sodium salt) and 0.5g of tazobactam (as sodium salt).

What Piperacillin with Tazobactam looks like

Piperacillin with Tazobactam is a powder for solution for intravenous infusion.

Contents of the pack

The powder comes in a glass vial with a rubber cap and metal/plastic seal. 1, 2, 5, or 10 vials come in a box. Not all pack sizes may be marketed.

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK Only) Please be ready to give the following information:

Product Name	Reference Number
Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion.	29831/0329
Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion.	29831/0341

This is a service provided by the Royal National Institute of Blind People.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Wockhardt UK Limited, Ash Road North, Wrexham, LL13 9UF, UK.

Manufacturer: Laboratory Reig Jofre S.A., C/Jarama s/n Pol Ind, 45007, Toledo, Spain.

This leaflet was last revised in 05/2023

103276/8

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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	70mg piperacillin / 8.75mg tazobactam / kg every eight hours.

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

Use in children aged below 2 years

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

No data from controlled clinical studies are available.

Treatment duration

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

Route of administration

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

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

For reconstitution instructions, see section 6.6.

Pharmaceutical Particulars

List of excipients

None

Incompatibilities

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

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

Because of 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.

Shelf life

Unopened - 3 years

When reconstituted with water for injections or saline, reconstituted solutions will remain stable for 24 hours at 25°C and for 48 hours at 4°C.

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

Special precautions for storage

Unopened: Do not store above 25°C.

After reconstitution: Store at 2-8°C (see 6.3 Shelf Life).

Nature and contents of container

Packs of one, two, five and ten* Type II glass vial with butyl rubber stopper and aluminium/plastic seal.

*Not all pack sizes may be marketed.

Special precautions for disposal and other handling Intravenous use

Each vial of Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion should be reconstituted with 10ml of one of the diluents detailed below.

Each vial of Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion should be reconstituted with 20ml of one of the following diluents:

- Sterile water for injections
- 0.9% sodium chloride for injection.

To achieve effective reconstitution, invert and shake the vial thoroughly to detach any powder adhering to the walls prior to addition of the diluent. Add the solvent and shake until complete dissolution is achieved.

The reconstituted solution should be further diluted to at least 50ml with one of the reconstitution diluents, or with Dextrose 5% in Water.

Displacement Volume

Each gram of Piperacillin/Tazobactam Powder for Solution for Infusion has a displacement volume of 0.7ml.

Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion will displace 1.58ml.

Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion will displace 3.15ml.

The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration.

The solution should only be used if the solution is clear and free from particles.

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

Marketing Authorisation Holder

Wockhardt UK Limited, Ash Road North, Wrexham LL13 9UF

Marketing Authorisation Number

PL 29831/0329 (Piperacillin/Tazobactam 2g/0.25g Powder for Solution for Infusion)

PL 29831/0341 (Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion)

Date of First Authorisation/Renewal of Authorisation

17 April 2009.

Date of Revision of Text

November 2021

103276/8

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