


WOCKHARDT LIMITED

	PRODUCT NAME	PHYTON 4.5 g
	GENERIC NAME	Piperacillin and Tazobactam for Injection USP

SUMMARY OF PRODUCT CHARACTERISTIC (PRODUCT DATA SHEET)

1. NAME OF THE MEDICINAL PRODUCT

PHYTON 4.5 g
Piperacillin and Tazobactam for Injection USP

Strength PHYTON 4.5 g

Composition: Each vial contains:

Sterile Piperacillin Sodium USP
Equivalent to Piperacillin.....4.0g
Sterile Tazobactam Sodium
Equivalent to Tazobactam.....0.5g
Sodium.....8.9mEq(205 mg)

2. QUALITY AND QUANTITATIVE COMPOSITION

Ingredients	Specification	Label Claim	Qty. / Vial.
Sterile Piperacillin Sodium USP Equivalent to Piperacillin	USP	4.0 g	4.0 g
Sterile Tazobactam Sodium Equivalent to Tazobactam.Sodium	USP	0.5g	0.5g

3. P HARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS


4.1 Therapeutic indications:

Piperacillin/Tazobactam is indicated for the treatment of the following infections in adults and children over 2 years of age:

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.

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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

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

Adult and adolescent patients

Infections

The usual dose is 4 g Piperacillin / 0.5 g Tazobactam given every eight hours. For nosocomial pneumonia and bacterial infections in neutropenic patients,

The recommended dose is 4 g piperacillin / 0.5 g 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 4 g / 0.5 g
Every six hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection
	Complicated urinary tract infections (including pyelonephritis)
Every eight hours	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: 4 g / 0.5 g every eight hours

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< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours
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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

Dose in elderly patients

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

Paediatric population (2-12 years of age)Infections

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

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

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

No data from controlled clinical studies are available.

Treatment duration

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

Route of administration

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

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients. History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

4.4 Special warning 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. Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving

Piperacillin/Tazobactam If patients develop a skin rash they should be monitored closely and Piperacillin/Tazobactam discontinued if lesions progress. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin/Tazobactam, should be discontinued. 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

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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 a full blood count 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. This medicinal product contains 4.72 mmol (109 mg) of sodium per vial of powder for solution for infusion. To be taken into account by patients 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 Interactions

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 drugs 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.

Vancomycin

No pharmacokinetic interactions have been noted between Piperacillin/ Tazobactam and vancomycin.

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Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results, as with other penicillin's. 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

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 Piperacillin and tazobactam cross the placenta. Piperacillin/Tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in breast milk; tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination Piperacillin/ Tazobactam


4.7 Effects on ability to drive and use machine

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, nausea, vomiting and rash. In the following table, adverse reactions are listed by system organ class and Med DRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequency groupings

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as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1\ 000$ to $\leq 1/100$); rare ($\geq 1/10\ 000$ to $\leq 1/1\ 000$); very rare ($<1/10\ 000$); not known (cannot be estimated from the available data).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins, including beta-lactamase inhibitors.

ATC code: J01C R05

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.


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

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Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible. Piperacillin/Tazobactam is widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with noninflamed meninges, as with other penicillins.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite.

Tazobactam is metabolised to a single metabolite, which has been found to be microbiologically inactive.

Elimination

Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile. Following single or multiple doses of Piperacillin/Tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance. There are no significant changes in piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to reduce the 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

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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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C.

After reconstitution: Store at 2-8°C


Reconstitution information

Each vial of Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Infusion should be reconstituted with 10ml 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.

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

6.5 Nature and contents of container

30 ml Transparent Flint glass vial USP type-III, free from pyrogens. The container is closed by 20 mm grey butyl rubber stoppers (pre-autoclaved) and finally sealed with 20 mm colored flip off seal.

7 MARKETING AUTHORIZATION HOLDER:

Wockhardt limited

Wockhardt Towers
Bandra Kurla Complex,
Bandra (East), Mumbai,
Maharashtra 400051

8. MARKETING AUTHORIZATION NUMBERS:

TO BE ALLOCATED

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:

TO BE ALLOCATED

10 DATE OF REVISION OF THE TEXT : NOT APPLICABEL