National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

JAWAPIP

Piperacillin Sodium And Tazobactam Sodium For Injection USP 4.5gm

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial Contains:

Piperacillin Sodium USP

Equivalent to Piperacillin .....4 gm

Tazobactam Sodium

Equivalent to Tazobactum .....500 mg

Excipients with known effect:
Not Applicable

3. PHARMACEUTICAL FORM

Powder for Injection

4. Clinical particulars

4.1 Therapeutic indications

Piperacillin Sodium and Tazobactam Sodium For Injection USP 4.5 gm is a combination penicillin-class antibacterial and β-lactamase inhibitor indicated for treatment of:

- Intra-abdominal infections
- Skin and skin structure infections
- Female pelvic infections
- Community-acquired pneumonia
- Nosocomial pneumonia
- Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin Sodium and Tazobactam Sodium For Injection USP 4.5 gm and other antibacterial drugs, Piperacillin Sodium and Tazobactam Sodium For Injection USP 4.5 gm should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

4.2 Posology and method of administration

The dose and frequency of Piperacillin and Tazobactam for Injection USP 4.5 gm depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients Infections

The usual dose is 4 g piperacillin and 0.5 g tazobactam given every eight hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin and 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 summarizes the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	**Piperacillin and Tazobactam for Injection USP**
	4.5 gm
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: 4 g / 0.5 g every eight hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 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.

following each dialysis period.

Use in children aged below 2 years

The safety and efficacy of Piperacillin and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP 4.5 gm is administered by intravenous infusion (over 30 minutes).

Each vial of Piperacillin and Tazobactam for Injection USP 4.5 gm should be reconstituted with 20 ml 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.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.

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

4.4 Special warnings and precautions for use

The selection of Piperacillin and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP 4.5gm, 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 and Tazobactam for Injection USP 4.5 gm. 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 lifethreatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin and Tazobactam for Injection USP 4.5 gm, should be discontinued.

Therapy with Piperacillin and Tazobactam for Injection USP 4.5 gm may result in the emergence of resistant organisms, which might cause superinfections.

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 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 9.44 mmol (217 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 interaction

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

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 and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP 4.5 gm with aminoglycosides.

Vancomycin

No pharmacokinetic interactions have been noted between Piperacillin and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP

4.5gm 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 and Tazobactam for Injection USP 4.5 gm. 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 and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP 4.5 gm 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 and Tazobactam for Injection USP 4.5 gm.

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

Undesirable effects are listed by frequency as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

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

Body system	**Frequency**	**Adverse Reaction**
Infections and infestations	Uncommon	Candidal superinfection
Blood and lymphatic system disorders	Uncommon	Leucopenia, neutropenia, thrombocytopenia
	Rare	Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia
	Very rare	Agranulocytosis, Coombs' direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis
Immune system disorders	Uncommon	Hypersensitivity reaction
	Rare	Anaphylactic /anaphylactoid reaction (including shock)
Metabolism and nutritional disorders	Very rare	Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia.
Nervous system disorders	Uncommon	Headache, insomnia
	Rare	Muscular weakness, hallucination, convulsion
Vascular disorders	Uncommon	Hypotension, phlebitis, thrombophlebitis
	Rare	Flushing
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomi ting
	Uncommon	Constipation, dyspepsia, jaundice, stomatitis
	Rare	Abdominal pain, pseudomembranous colitis, dry mouth

Hepatobiliary disorders	Uncommon	Alanine aminotransferase increased, aspartate aminotransferase increased
	Rare	Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash
	Uncommon	Pruritus, urticaria, erythema
	Rare	Bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema
	Very rare	Stevens-Johnson Syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, myalgia
Renal and urinary disorders	Uncommon	Blood creatinine increased
	Rare	Interstitial nephritis, renal failure
	Very rare	Blood urea nitrogen increased
General disorders and administration site conditions	Uncommon	Fever, injection site reaction
	Rare	Rigors, tiredness, oedema

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

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

4.9 Overdose

There have been postmarketing reports of overdose with Piperacillin/Tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhea, have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure

Treatment should be supportive and symptomatic according the patient's clinical presentation.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis. Following a single 3.375 g dose of piperacillin/tazobactam, the percentage of the piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS

Pharmacotherapeutic group: Combinations of penicillins, including beta- lactamase inhibitors ATC Classification: J01CR05

Mechanism of action:

Piperacillin, a broad spectrum, semi-synthetic penicillin active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the Piperacillin and Tazobactam for Injection USP 4.5 gm formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, Piperacillin and Tazobactam for Injection USP 4.5 gm combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Mechanism of resistance:

The presence of tazobactam expands the spectrum of activity of piperacillin to include microorganisms that would otherwise, due to the formation of beta- lactamase, be resistant to piperacillin and other beta-lactam antibiotics. In vitro investigation has demonstrated that the type I beta-actamase inducing ability of tazobactam is insignificant with regard to Gram-negative bacteria. In vitro studies have demonstrated a synergetic effect of Piperacillin and Tazobactam for Injection USP 4.5 gm and aminoglycosides against Pseudomonas aeruginosa and other bacteria, including beta-lactamase producing strains.

Breakpoints:

The minimum inhibitory concentration (MIC) breakpoints separating susceptible, intermediately susceptible and resistant organisms have been defined as follows:

Pathogen	**Species-related breakpoints (S < / R >)** (For susceptibility testing the concentration of tazobactam is fixed at 4 mg/l)
Enterobacteriaceae	8/16
Pseudomonas aeruginosa	16/16
Gram-negative and Gram- positive anaerobes	8/16
Staphylococcus Methicillin-susceptible strains Methicillin-resistant strains	S R
Non-species related break- points	4/16

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

Commonly susceptible species

Gram positive aerobes

Brevibacterium spp

Enterococcus faecalis

Listeria monocytogenes

Staphylococcus spp. methicillin-sensitive Streptococcus

pneumoniae Streptococcus pyogenes

Group B streptococci Streptococcus spp*

Gram negative aerobes

Branhamella catarrhalis

Citrobacter koseri

Haemophilus influenzae*

Haemophilus spp.

Proteus mirabilis

Salmonella spp.

Shigella spp.

Gram positive anaerobes

Clostridium spp.

Eubacterium spp.

Peptococcus spp.

Peptostreptococcus spp.

Prevotella spp*

Gram negative anaerobes

Bacteroides fragilis*

Bacteroides fragilis group

Fusobacterium spp.

Porphyromonas spp.

Species for which resistance may be a problem

Gram positive aerobes

Staphylococcus aureus, methicillin-sensitive

Staphylococcus epidermis, methicillin-sensitive

Enterococcus avium ($)

Enterococcus faecium (+ $)

Propionibacterium acnes ($)

Viridans streptococci

Gram negative aerobes

Actinobacter spp (+ $)

Burkholderia cepacia

Citrobacter freundii

Enterobacter spp.

Escherichia coli *

Klebsiella spp.

Proteus, indole positive

Pseudomonas aeruginosa*

Pseudomonas spp. *

Pseudomonas stutzeri $

Serratia spp.

Gram negative anaerobes

Bacteroides spp. *

Inherently resistant organisms Gram positive aerobes

Corynebacterium jeikeium

Staphylococcus spp. methicillin resistant

Gram negative aerobes

Legionella spp

Stenotrophomonas maltophilia +$

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

($)Species showing natural intermediate susceptibility

(+) Species for which high resistance rates (more than 50%) have be en observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic properties

1.2 Distribution

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

There is a greater proportional (approximately 28%) increase in plasma levels of piperacillin and tazobactam with increasing dose over the dosage range of Piperacillin and Tazobactam for Injection USP 2.5 gm to Piperacillin and Tazobactam for Injection USP 4.5 gm.

Both piperacillin and tazobactam are 20 to 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and Tazobactam for Injection USP 4.5 gm is widely distributed in tissue and body fluids including intestinal mucosa, gall bladder, lung, bile and bone.

Biotransformation

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

Elimination

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

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

Following single or multiple doses of Piperacillin and Tazobactam for Injection USP 4.5 gm to healthy subjects, the plasma half -life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

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

Impaired renal function:

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

Impaired liver function:

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

Paediatric patients

The pharmacokinetics of Piperacillin and Tazobactam for Injection USP 4.5 gm has been studied in paediatric patients with intra-abdominal infections and other kinds of infections. In every age group, renal fraction of elimination of piperacillin and tazobactam was approximately 70% and 80%, respectively, like in adults.

Mean pharmacokinetic parameters of Piperacillin and Tazobactam for Injection USP 4.5 gm of paediatric patients of different age groups.

Piperacillin			**Tazobactam**	
Age group	**Half-life**	**Clearance (ml/min/kg)**	**Half-life**	**Clearance (ml/min/kg)**
2-5 years	0.7	5.5	0.8	5.5
6-12 years	0.7	5.9	0.9	6.2

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not Applicable

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except Sterile water for injections and 0.9% sodium chloride for injection.

Whenever Piperacillin and Tazobactam for Injection USP 4.5 gm is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of Piperacillin and Tazobactam for Injection USP 4.5 gm with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin and Tazobactam for Injection USP 4.5 gm should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Because of chemical instability, Piperacillin and Tazobactam for Injection USP 4.5 gm should not be used with solutions containing only sodium bicarbonate.

Lactated Ringer's solution is not compatible with Piperacillin and Tazobactam for Injection USP 4.5 gm.

Piperacillin and Tazobactam for Injection USP 4.5 gm should not be added to blood products or albumin hydrolysates

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C in a dry place.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

30 ml Plain Glass Vial (USP Type- I) packed in the carton along with Sterilized water for Injections BP 10 ml (2 ampoules) along with insert

6.6 Special precautions for disposal <and other handling>

Not Applicable

7. APPLICANT

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