SUMMARY OF PRODUCT CHARACTERISTICS:

1. Name of the Finished Pharmaceutical product

1.1 Product Name
TAZIP- 4.5
Piperacillin and Tazobactam for Injection USP

1.2 Strength
4500 mg

1.3 Pharmaceutical Dosage Form
Dry powder for Injection

2. Qualitative and quantitative composition
Each vial contains:
Piperacillin Sodium USP (Sterile)
Equivalent to Piperacillin …… 4 g
Tazobactam Sodium (Sterile)
Equivalent to Tazobactam ... 500 mg
Sodium 8.9 mEq (205 mg)

3. Pharmaceutical Form

Dry Powder for Injection.

4. Clinical Particulars
4.1 Therapeutic Indications
Piperacillin/ Tazobactam is indicated for following 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 bacteremia 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 some bacterial infections.

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's 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 summarizes the treatment frequency and the recommended dose for adults and adolescent patients by indication or condition:

Treatment Frequency	**Piperacillin/ Tazobactam 4g/0.5g**
Every six hours	Severe pneumonia
	Neutropenic adults with severe suspected to be due to a bacterial infection
Every eight hours	Complicated urinary tract infections
	Complicated intra – abdominal infections
	Skin and soft tissue 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 products 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 twelve hours

For patients on hemodialysis, one additional dose of Piperacillin/Tazobactam 2g/0.25 g should be administered following each dialysis period, because hemodialysis 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

Pediatric population (2- 12 years of age)
Infections
The following table summarizes the treatment frequency and the dose per body weight for pediatric patients 2 – 12 years of age by indication or conditions

Dose per weight and treatment frequency	Indication/condition
80 mg Piperacillin/10mg 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 six hours	Complicated intra – abdominal infections

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

Renal impairment
The intravenous dose should be adjusted to the degree of actual renal impairment as follow

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
>50	No dose adjustment required
<50	70 mg Piperacillin/ 8.75 mg Tazobactam /kg every eight hours

For children hemodialysis, one additional dose of 40 mg 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 patients clinical and bacteriological progress.

Route of administration

Piperacillin/Tazobactam 2g /0.25 g is administered by intravenous infusion (over 30 minutes)
Piperacillin/Tazobactam 4g /0.5 g is administered by intravenous infusion (over 30 minutes)

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin – antibacterial agents or to any of the excipients
History of acute severe allergic reaction to any other beta – lactam active substances

4.4 Special warnings and precautions for use

The selection of Piperacillin/Tazobactam to treat an individual patient should take into account the appropriateness of using a broad spectrum semi – synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.
Before initiating therapy with piperacillin/Tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta – lactam agents and other allergens. Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving therapy with penicillin, 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 Steven – 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 diarrhea, 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 abnormal 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 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 penicillin, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

This medical product contains certain amount of sodium per vial of powder for solution for infusion. To be taken into account by patients on a controlled sodium diet.
Hypokalemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determination may be advisable in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

Non – depolarising muscle relaxants
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non –depolarising muscle relaxants could be 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 penicillin, concurrent administration of probenecid and Piperacillin/Tazobactam produces a longer half-life and lower renal clearance for both piperacillin Tazobactam; however, peak plasma concentration of either substance 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 gentamycin by piperacillin has been demonstrated in patients with severe renal impairment

Vancomycin
No pharmacokinetics interaction has been noted between Piperacillin/Tazobactam and vancomycin. However, a limited number of retrospective studies have detected an increased incidence of acute kidney injury in patients concomitantly administered Piperacillin/Tazobactam and vancomycin as compared to vancomycin alone

Effects on laboratory tests
Non – enzymatic methods of measuring urinary glucose may lead to false – positive results as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Piperacillin/Tazobactam therapy. 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 tests have been reported.
Positive tests result for the assays listed above in patients receiving Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or 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 benefits outweigh the possible risk to the pregnant women 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 benefits outweigh the possible risks to the woman and the child.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported adverse reaction is diarrhea, nausea, vomiting and rash.
Among the most serious adverse reactions pseudo – membranous colitis and toxic epidermal necrolysis
occur in 1 to 10 patients in 10,000. The frequency of pancytopenia, anaphylactic shock and Steven – Johnson syndrome cannot be estimated from the currently available data.
In the following table, adverse reactions are listed by system organ class and MedDRA – preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Very common** ≥1/10	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <1/100	**Rare** ≥1/10,000 to <1/1,000	**Frequency not known** (cannot ne estimated from available data
Infections and Infestation		candidiasis			
Blood and lymphatic system disorders		Thrombocytopenia, anemia, coombs direct test positive, activated partial thromboplastin time prolonged	Leukopenia, prothrombin time prolonged	Agranulocytosis, epistaxis	Pancytopenia, neutropenia, purpura, bleeding time prolonged, hemolytic anemia, eosinophilia, thrombocytosis
Immune system disorder					Anaphylactic reaction, anaphylactoid shock, anaphylactic shock, hypersensitivity
Metabolism and nutrition disorder		Blood albumin decreased, protein total decreased	Hypokalemia, blood glucose decreased		
Nervous system disorder		Headache, insomnia			
Vascular disorder			Hypotension, thrombophlebitis, phlebitis, flushing		
Gastrointestinal Disorders	Diarrhea	Abdominal pain, vomiting, nausea, constipation, dyspepsia		Pseudo-membranous colitis, stomatitis	
Hepatobiliary disorders		Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased	Blood bilirubin increased		Hepatitis, jaundice, gamma – glutamyltransferase increased
Skin and subcutaneous tissue disorders		Rash, pruritus	Erythema, multiforme, urticarial, rash maculopapular	Toxic epidermal necrolysis	Steven – Johnson syndrome, dermatitis bullous
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia		
Renal and urinary disorder		Blood creatinine increased, blood urea increased			Renal failure, tubulointestinal nephritis
General disorders and administration site conditions		Pyrexia, injection site reaction	chills		

Reporting of suspected adverse reaction: Healthcare professional are requested to report any suspected adverse reaction to the National Regulatory Agents.

4.9 Overdose

Symptoms

There has been post – marketing 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 dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously

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 patient's clinical presentation

Excessive serum concentrations of either piperacillin or Tazobactam may be reduced by hemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antibacterial for systemic use, Combination of penicillins, including beta – lactamase inhibitors

ATC Code: J01CR05

Mechanism of action

Piperacillin, a broad spectrum, semisynthetic penicillin exerts bactericidal activity by inhibtion of both septum and cell wall sythesis.

Tazobactam, a beta- lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause rsistance to penicillins and cephalosporins but it does not inhibit AmpC enzyme or metallo beta – lactamases.

Tazobactam extends the antibiotic spectrum of Piperacillin to include many beta – lactamnase producing bacteria that have acquired resistance to Piperacillin alone.

5.2 Pharmacodynamics properties

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamics determinant of efficacy for Piperacillin.

Breakpoints:

EUCAST clinical MIC breakpoints

For Susceptibility testing purpose, the concentration of Tazobactam is fixed at 4 mg/L

Pathogens	Species – related breakpoints
Enterpbacteriaceae	8/16
Pseudomonas	16/16
Gram – negative and Gram – positive anaerobes	8/16
Non – species related breakpoint	4/16

The susceptibility of streptococci is inferred from the penicillin susceptibility

Susceptibility

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

Commonly susceptible species

Gram positive aerobes
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus aureus, methicillin susceptible
Staphylococcus species, coagulase negative, methicillin – susceptible
Streptococcus pyrogens
Group B Streptococci
Gram negative aerobes
Citrobacter koseri
Haemophilus influenza
Moraxella catarrhalis
Proteus mirabilis
Gram positive anaerobes
Clostridium spp.
Eubacterium spp.
Peptostreptococcus spp.
Gram negative anaerobes
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.
Species for which acquired resistance may be a problem
Enterococcus faecium
Streptococcus pneumonia
Streptococcus viridans group
Gram negative aerobes
Actinobacter baumannii
Burkholderia cepacia
Citrobacter freundii
Enterobacter spp.
Escherichia coli
Klebsiella pneumonia

Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia spp.
Gram positive aerobes
Corynebacterium jeikeim
Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilla
Other microorganisms
Chlamydophilla pneumonia
Mycoplasma pneumonia
Species showing natural intermediate susceptibility
Species for which high resistance rates have been observed in one or more areas/countries/ regions within the EU
All methicillin – resistant staphylococci are resistant to piperacillin/Tazobactam.

5.3 Pharmacokinetics properties

Absorption
The peak piperacillin and Tazobactam concentrations after 4g/0.5g administered over 30 minutes by intravenous infusion are 298µg/ml and 34 µg/ml respectively.

Distribution
Both Piperacillin and Tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or Tazobactam is unaffected by the presence of the other compound. Protein binding of the Tazobactam metabolite is negligible.
Piperacillin/Tazobactam, is widely distributes 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 non- inflamed meninges, as with other penicillins.

Biotransformation
Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolite 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/Tazobactam to healthy subjects, the plasma half piperacillin and Tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or

duration of infusion. The elimination half live of both piperacillin and Tazobactam are increased with decreased renal function.
There are no significant changed 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 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy patients.
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 20ml/min compared to patients with normal renal function.
Hemodialysis 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 dose, respectively, with up to 18% of the Tazobactam dose removed as the Tazobactam metabolite.

Pediatric population
In a population Pk analysis, estimated clearance for 9 months old to 12-year-old patient 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 pediatric patients 2-9months of age. The population mean (SE) for Piperacillin volume of distribution is 0.243 (0.11) l/kg and is independent of age.

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

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

5.4 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and Geno toxicity. Carcinogenicity studies have not been conducted with Piperacillin/Tazobactam.
A fertility and general reproduction study in rats using intraperitoneal administration of Tazobactam or the combination therapy Piperacillin/Tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variation of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.
Teratogenicity studies using intravenous administration of Tazobactam or the combination Piperacillin/Tazobactam in mice and rats resulted in slight reductions in rat foetal weights at maternally toxic doses but did not show teratogenic effects.
Peri/Post-natal development was impaired concurrently with maternal toxicity after intraperitoneal administration of Tazobactam or in Combination of Piperacillin/Tazobactam in the rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned. Whenever Piperacillin/Tazobactam is used concurrently with another antibiotic, 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

When reconstituted with water for Injections or saline, reconstituted solution 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.

6.4 Special precautions for storage

Unopened: Store below 25°C. protect from light.
After reconstitution: Store at 2- 8°C

6.5 Nature and contents of container

30 mL Tubular glass vial USP Type III, stoppered with 20 mm Grey Butyl Rubber plugs and sealed with 20 mm Flip off Seal, suitably labeled and packed in printed carton along with patient information leaflet.

6.6 Special precautions for disposal and other handling

Intravenous Use
Each vial of Piperacillin/Tazobactam 2g/0.25g and 4g/0.5g Powder for Solution for Infusion should be reconstituted with 10 ml and 20 ml respectively 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 50 ml with one of the reconstitution diluents, or with dextrose 5% in water.
Displacement volume
Each gram of Piperacillin/Tazobactam 2g/0.25g and 4g/0.5g 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 4g/Tazobactam 0.5g Powder for Solution for infusion will displace 3.15 ml
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 products or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site address

Marketing authorization holder:

Company name: INNOCIA LIFESCIENCES FZE LLC
Address: A-0059-508 Flamingo Villas, Ajman Country: United Arab Emirates.
Telephone: +91 9003085554
E-Mail: innocia1997@gmail.com

Manufacturing site address

Company Name: Zeiss Pharmaceuticals Pvt. Ltd.
Address: 72 Export promotion Industrial Park Phase –I Jharmajri, Baddi Distt. Solan (H.P.)
Mob. No: 9218548704
E-mail : **qualitycontrol@zpharma.co.in**

8. Marketing authorization number(s)

CTD12055

9. Date of first authorization/renewal of the authorization

23//07/2026

10. Date of revision of the text

23//07/2026