1.17 Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT
PIPCEL 4.5 INJECTION (PIPERACILLIN & TAZOBACTAM FOR INJECTION USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Vial Contains:
Piperacillin Sodium USP equivalent to
Piperacillin ……..…4000 mg
Tazobactam Sodium USP equivalent to
Tazobactam…….500 mg

3. PHARMACEUTICAL FORM
Powder for Injection
A white crystalline powder filled in clear glass sealed vials.

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.

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 localisation of the infection and expected pathogens.

Adult and adolescent patients Infections

The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 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/Tazobactam4g/0.5g**
Every6hours	Severepneumonia
	Neutro penic adults with fever suspected to be due to a bacterial
Every8hours	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 as follows (each patient must be monitored closely for signs of substanc e 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/0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 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 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	Indication/condition
80 mg Piperacillin/10mgTazobactam per kg body weight /every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100mg Piperacillin/12.5 mgTazobactam per kg body weight /every 8 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 (recommendeddose)
>50	No dose adjustment needed.
≤50	70 mg piperacillin/8.75mg tazobactam/kg every 8 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

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 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes). 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 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 (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, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis have been reported in patients receiving Piperacillin/Tazobactam (see section 4.8). 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 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.

Renal Impairment

Due to its potential nephrotoxicity (see section 4.8), piperacillin/tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment (see section 4.2).

In a secondary analysis using data from a large multicenter, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these 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 mechanism 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 substances , which 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. 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

For information related to administration of piperacillin/tazobactam with aminoglycosides please refer to section 6.2 and 6.6.

Vancomycin

No pharmacokinetic interactions have been noted between piperacillin / tazobactam 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/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 andpolyfuranoses 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 Fertility, 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 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 reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

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	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000),
Infections and infestations:		Candidalsuperinfection		
Blood and lymphatic system disorders:		leucopenia, neutropenia, thrombocytopenia	anaemia, purpura, epistaxis, bleeding time prolonged) eosinophilia, haemolyticanaemia	agranulocytosis, Coombs direct test positiv, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, thrombocythaemia
Immune system disorders:		Hypersensitivity	anaphylactic / anaphylactoid reaction	

			(including shock)	
Metabolism and nutrition disorders				blood glucose decreased, blood albumin decreased, blood protein total decreased hypokalaemia
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, phlebitis, thrombophlebitis	Flushing	
Gastrointestinal disorders	diarrhoea, nausea, vomiting	constipation, dyspepsia, jaundice, stomatitis	abdominal pain, pseudomembra-nous colitis,	
Hepatobiliary disorders		alanine aminotransferase increased, aspartate aminotransferase increased	Blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransfera se increased, hepatitis	
Skin and subcutaneous tissue disorders	Rash including maculopapul ar rash	pruritus, urticaria,	bullous dermatitis, erythema multiforme, exanthema	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeleta l, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary		blood creatinine increased	tubulointerstitial nephritis, renal	blood urea increased

disorders			failure	
General disorders and administration site conditions		pyrexia,, injection site reaction	chills	

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

4.9 Overdose, symptoms, emergency procedures and antidotes

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

Mechanism of action

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

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

Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / 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.

Breakpoints

EUCAST clinical MIC breakpoints 2009 (2009-12-02, v 1):

For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L

Pathogen	**Species-related breakpoints (S≤/R>)**
Enterobacteriaceae	8/16
Pseudomonas	16/16
Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

The susceptibility of *streptococci* is inferred from the penicillin susceptibility.

The susceptibility of *staphylococci* is inferred from the oxacillin 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 of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to piperacillin / tazobactam susceptibility

Commonly susceptible species

Gram positive aerobes

Enterococcus faecalis

Listeria monocytogenes

Staphylococcus aureus, methicillin susceptible[£]

Staphylococcus species, *coagulase negative,* methicillin-susceptible

Streptococcus pyogenes

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

Gram positive aerobes

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.

Inherently resistant organisms

Gram positive aerobes

Corynebacterium jeikeium

Gram negative aerobes

Legionella spp

Stenotrophomonas maltophilia [+,$]

Other microorganisms

Chlamydophilia pneumonia

Mycoplasma pneumonia

[$] Species showing natural intermediate susceptibility

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

[£] All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

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

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 non-inflamed 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 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-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

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.

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination Piperacillin/Tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations 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 fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after intraperitoneal administration of tazobactam or the combination Piperacillin/ Tazobactam in the rat.

6. Pharmaceutical particulars

6.1 List of excipients

No Excipient used.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 Months.

6.4 Special precautions for storage
Store below 30°C and protect from light.

6.5 Nature and contents of container
30 ml Glass vial

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. MARKETING AUTHORIZATION HOLDER
Applicant:

NATIONAL PHARMACY LIMITED

P.O.BOX 17843 – 00500,

NAIROBI, KENYA.

Manufacturer:

Systochem Laboratories Ltd.

B-75, Roop Nagar, Industrial Area,

Loni-201 102 (UP) (India)

8. MARKETING AUTHORIZATION NUMBER(S)
Not applicable

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Not applicable

10. DATE OF REVISION OF THE TEXT:
30 February. 2022