APPROVED Professional Information for CINOTAZ

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CINOTAZ 2 powder for solution for infusion

CINOTAZ 4 powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CINOTAZ 2 infusion contains piperacillin sodium equivalent to piperacillin 2 g and tazobactam sodium equivalent to tazobactam 250 mg.

CINOTAZ 4 infusion contains piperacillin sodium equivalent to piperacillin 4 g and tazobactam sodium equivalent to tazobactam 500 mg.

Sugar free.

Excipients with known effect:

Each CINOTAZ 2 vial contains 128 mg sodium

Each CINOTAZ 4 vial contains 256 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white powder. Reconstituted solution: Clear colourless solution free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CINOTAZ is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Adults

1. Community acquired pneumonia due to *Haemophilus influenza.*
2. Intra-abdominal infections caused by piperacillin resistant beta-lactamase producing strains of *Escherichia coli* and *Bacteroides fragilis.*
3. Skin and skin structure infections caused by piperacillin resistant beta-lactamase producing strains of *Staphylococcus aureus.*
4. Gynaecologic infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *E. coli.*
5. CINOTAZ plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children

Children under the age of 12 years:

CINOTAZ plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children 2 to12 years:

In hospitalised children aged 2 to 12 years, CINOTAZ is indicated for the treatment of serious intra-abdominal infections, caused by *E. coli* or *Bacteroides* species. CINOTAZ has not been evaluated in this indication for paediatric patients below the age of 2 years.

While CINOTAZ is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to CINOTAZ treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and beta-lactamase producing organisms susceptible to CINOTAZ should not require the addition of another antibiotic.

CINOTAZ is useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests.

4.2 Posology and method of administration

Posology

Adults and children 12 years and older:

The usual dosage for adults and children with normal renal function is CINOTAZ 4 (4/0,5 g) given every eight hours. The dosage in immuno-compromised and neutropenic patients with infection is CINOTAZ 4 (4/0,5 g) every six hours in combination with an aminoglycoside.

Neutropenic patients:

In treating neutropenic patients, full therapeutic doses of CINOTAZ and an aminoglycoside should be used. The possibility of hypokalaemia should be kept in mind in patients who have low potassium reserves, and periodic electrolyte determinations should be made in these patients.

Duration of therapy:

In acute infections, treatment with CINOTAZ should be for a minimum of five days and continued for forty-eight hours beyond resolution of clinical symptoms of the fever. The usual duration of treatment is 7 – 10 days.

Special populations

Elderly:

CINOTAZ may be used at the same dose levels as adults except in cases of renal impairment (see below).

Renal insufficiency:

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal function impairment. The suggested daily doses are as follows:

Intravenous dosage schedule for adults with impaired renal function:

Creatinine clearance (mL/min)	**Recommended CINOTAZ (piperacillin/tazobactam) dosage**
90 – 40	12 g/1,5 g per day in divided doses of 4 g/0,5 g every 8 hours or 3 g/0,375 g every 6 hours
20 – 40	8 g/1,0 g per day in divided doses of 2 g/0,25 g every 6 hours
< 20	6 g/0,75 g per day in divided doses of 2 g/0,25 g every 8 hours

For patients on haemodialysis, the maximum daily dose is CINOTAZ 2 (2 g/0,25 g piperacillin/tazobactam) every 8 hours. In addition, because haemodialysis removes 30 – 40 % of piperacillin in four hours, one additional dose of 0,75 g piperacillin/tazobactam should be administered following each dialysis period.

For patients with renal failure and hepatic insufficiency, measurement of serum levels of piperacillin and tazobactam will provide additional guidance for adjusting dosage.

Paediatric population

Children under the age of 12 years:

CINOTAZ is only recommended for the treatment of children with neutropenia.

For children weighing over 50 kg, follow the adult dosing guidance, including the aminoglycoside.

For children with normal renal function and weighing less than 50 kg, the dose should be adjusted to 90 mg/kg (80 mg piperacillin / 10 mg tazobactam) administered every six hours, in combination with an aminoglycoside.

Hospitalised children with intra-abdominal infection:

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dosage is 112,5 mg/kg (100 mg piperacillin/12,5 mg tazobactam) every 8 hours.

For children aged 2 to 12 years weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. 4,5 g (4 mg piperacillin/0,5 mg tazobactam) every 8 hours.

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Therapy is recommended to be a minimum of 5 days and a maximum of 14 days, considering the dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

Children aged 2 – 12 years with renal insufficiency:

The pharmacokinetics of CINOTAZ has not been studied in paediatric patients with renal impairment. The following dosage adjustment for paediatric patients aged 2 to 12 years with renal impairment is recommended.

Intravenous dosage schedule for children aged 2 – 12 years with impaired renal function:

Creatinine clearance (mL/min)	**Recommended CINOTAZ (piperacillin/tazobactam)**

	dosage
> 50	112,5 mg/kg (100 mg/12,5 mg) every 8 hours
≤ 50	78,75 mg/kg (70 mg/8,75 mg) every 8 hours

The dosage modification is only an approximation. Each patient must be monitored closely for signs of toxicity. Dosage and interval should be adjusted accordingly.

Method of administration

For intravenous infusion.

CINOTAZ must be given by slow intravenous infusion (30 minutes)

4.3 Contraindications

The use of CINOTAZ is contraindicated in:

- Patients with a known hypersensitivity to piperacillin, tazobactam or any of the excipients of CINOTAZ (listed in section 6.1).
- Patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamase inhibitors.

4.4 Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome): Haemophagocytic lymphohistiocytosis (HLH) may occur, and have been reported in patients treated with CINOTAZ, often following treatment longer than 10 days. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation.

Patients should be carefully monitored and if any abnormalities such as pyrexia, rash, neurological

symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of CINOTAZ should be discontinued, and appropriate measures should be taken.

In patients receiving therapy with penicillin, serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid including shock) reactions have been reported. These reactions are more relevant to occur in persons with a history of penicillin hypersensitivity or sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity that have experienced severe hypersensitivity reactions when treated with cephalosporin. Before initiating therapy with CINOTAZ, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

If an allergic reaction occurs during therapy with CINOTAZ, the antibiotic should be discontinued. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). Serious hypersensitivity reactions require immediate emergency measures, with epinephrine (adrenaline), corticosteroids and antihistamines. An open airway must be maintained.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving CINOTAZ (see section 4.8). If patients develop a skin rash they should be monitored closely and CINOTAZ discontinued if lesions progress.

Pseudomembranous colitis has been reported. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis may occur during or after antibacterial treatment. Therefore, it is

important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial medicines.

Therapeutic measures should be initiated after the diagnosis of pseudomembranous colitis has been established. Mild cases of pseudomembranous colitis usually respond to CINOTAZ discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial medicine effective against *C. difficile.*

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced life-threatening pseudomembranous colitis must be taken into consideration. Therefore, CINOTAZ must be discontinued immediately in such cases and suitable therapy be initiated (e.g. oral teicoplanin or oral vancomycin). Preparations, which inhibit peristalsis, are contraindicated.

During prolonged therapy leukopenia and neutropenia may occur. For this reason, periodic assessment of haematopoietic function should be performed.

Periodic assessment of organ system functions, including renal and hepatic, during prolonged therapy is advisable.

If bleeding manifestations occur, CINOTAZ should be discontinued and appropriate therapy instituted. These reactions have sometimes 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 impairment.

While CINOTAZ possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal and hepatic during prolonged

therapy is advisable.

Patients may experience neuromuscular excitability or convulsions if higher than recommended doses of CINOTAZ are given intravenously, especially in patients with impaired renal function.

The use of CINOTAZ may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

In patients with renal insufficiency or haemodialysis patients, the intravenous dose of CINOTAZ should be adjusted to the degree of renal function impairment.

Patients over 65 years are not at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency (see section 4.2).

The possibility of the emergence of resistant organisms, which might cause superinfections, should be kept in mind, particularly during prolonged treatment with CINOTAZ. If this occurs, appropriate measures should be taken.

CINOTAZ contains sodium:
CINOTAZ 2 contains 128 mg sodium per vial, equivalent to 6,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
CINOTAZ 4 contains 256 mg sodium per vial, equivalent to 13 % of the WHO recommended maximum daily intake of 2 g for an adult.

Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalaemia should be kept in mind with patients who have potentially low

potassium reserves and who are receiving cytotoxic therapy or diuretics. Modest elevation of indices of liver function may be observed.

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines

Probenecid:

Concurrent administration of probenecid and CINOTAZ produced a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either medicine are unaffected.

Vancomycin:

No interaction is found between CINOTAZ and vancomycin.

Oral anticoagulants:

During simultaneous administration of high doses of heparin, oral anticoagulants and other medicines that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested more frequently and monitored regularly.

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 such as vecuronium could be prolonged in the presence of piperacillin.

Methotrexate:

Serum levels of methotrexate should be monitored in patients to avoid medicine toxicity, as CINOTAZ may reduce the excretion of methotrexate.

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 / tazobactam with aminoglycosides please refer to sections 6.2 and 4.2.

Concurrent use of other hepatotoxic medication with CINOTAZ may increase the potential for hepatotoxicity.

Interactions with laboratory tests and investigations

The use of CINOTAZ may result in a false-positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used. There have been reports of positive test results using the Bio-Rad Laboratories *Platelia Aspergillus* EIA test in patients receiving CINOTAZ injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported. For this reason, positive test results in patients receiving CINOTAZ should be interpreted carefully and confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Both piperacillin and tazobactam cross the placenta.

Breastfeeding

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women receiving CINOTAZ should not breastfeed their infants.

Fertility

Preclinical studies showed no effect on fertility and reproduction 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

Infections and infestations

Less frequent: Candida super-infections.

Frequency unknown: False positive tests for *Aspergillus* infection.

Blood and lymphatic system disorders

Frequent: Thrombocytopenia, positive Coombs direct test (antiglobulin test), prolonged activated partial thromboplastin time.

Less frequent: Leukopenia, epistaxis, agranulocytosis, prolonged prothrombin time (increased INR).

Frequency unknown: Neutropenia, purpura, prolonged bleeding time.

Metabolism and nutritional disorders

Less frequent: Decreased blood albumin, decreased blood glucose, decreased blood total protein, hypokalaemia.

Psychiatric disorders

Less frequent: Agitation, confusion, anxiety, hallucination, depression.

Nervous system disorders

Less frequent: Headache, insomnia, seizures.

Vascular disorders

Less frequent: Hypotension, phlebitis, thrombophlebitis, flushing.

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, constipation, dyspepsia, abdominal pain.

Less frequent: Stomatitis, pseudomembranous colitis.

Hepato-biliary disorders

Frequent: Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase.

Less frequent: Increased bilirubin.

Frequency unknown: Jaundice, increased gamma-glutamyl transferase.

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus.

Less frequent: Urticaria, exanthema.

Frequency unknown: Bullous dermatitis.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia.

Renal and urinary disorders

Less frequent: Increased blood creatinine, increased blood urea, dysuria.

Frequency unknown: Renal failure.

General disorders and administration site conditions

Frequent: Fever, injection site reaction, rigors.

Less frequent: Chills.

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

Post-marketing:

The following post marketing adverse events have been reported with the combination piperacillin/tazobactam:

Infections and infestations

Candidiasis.

Blood and lymphatic system disorders

Anaemia, pancytopenia, haemolytic anaemia, eosinophilia, thrombocytosis.

Psychiatric disorders

Delirium.

Immune system disorders

Hypersensitivity reaction, anaphylactic/anaphylactoid reaction (including shock).

Cardiac disorders

Kounis syndrome.

Hepato-biliary disorders

Hepatitis.

Skin and subcutaneous tissue disorders

Erythema multiforme, maculopapular rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), linear IgA disease.

Renal and urinary disorders

Tubulointerstitial nephritis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CINOTAZ is important. It allows continued monitoring of the benefit/risk balance of CINOTAZ. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Symptoms of overdosage include nausea, vomiting and diarrhoea (see sections 4.8 and 4.4). These side effects have also been reported with the usual recommended dosages. Patients may

experience neuromuscular excitability of convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

Treatment should be supportive and symptomatic according to the patient's clinical presentation. No specific antidote is known. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

In the case of motor excitability or convulsions, anticonvulsive medicines (e.g. diazepam of barbiturates) may be indicated.

In case of severe, hyperallergic (anaphylactic) reactions, the usual countermeasures are to be initiated (antihistamines, corticosteroids, symphatomimetic medicines and, if required, oxygen and airway management).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

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

ATC code: J01C R05.

The injectable antibacterial combination consists of the semi-synthetic antibiotic piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium.

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 an 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/tazobactam 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/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

The presence of tazobactam expands the spectrum of activity of piperacillin to include micro-organisms that would otherwise, due to the formation of beta-lactamase, be resistant to piperacillin and other beta-lactam antibiotics.

In vitro studies have demonstrated a synergistic effect of piperacillin/tazobactam and aminoglycosides against *Pseudomonas aeruginosa* and other bacteria, including beta-lactamase producing strains.

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: betalactamases 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 for piperacillin/ tazobactam (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 medicine in at least some types of infections is questionable.

Please note *in vitro* sensitivity does not necessarily imply clinical sensitivity.

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A

Approval date – 4 Feb 2025 (0006)

PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecium[$,+]
Streptococcus pneumonia
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii[$]
Burkholderia cepacia
Citrobacter freundii
Enterobacter species
Escherichia coli
Klebsiella pneumonia
Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Corynebacterium jeikeium
Aerobic Gram-negative micro-organisms
Legionella species
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

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.

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/ tazobactam are widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, 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 microbiologically inactive.

Elimination

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

secretion.

Piperacillin is rapidly excreted unchanged 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 unchanged 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. However, piperacillin reduces the rate of elimination of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam is increased in patients with hepatic cirrhosis compared to healthy subjects. Dosage adjustment of piperacillin is not warranted in patients with hepatic cirrhosis.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Whenever CINOTAZ is used concurrently with another antibiotic, especially an aminoglycoside, the medicines must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility (see section 4.2).

The mixing of beta-lactam antibiotics with aminoglycosides in vitro can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamycin were determined to be compatible with CINOTAZ *in vitro* in certain diluents at specific concentrations (see section 4.2).

CINOTAZ should not be mixed with other medicines in a syringe or infusion bottle since compatibility has not been established.

CINOTAZ should not be added to blood products or albumin hydrolysates.

Because of chemical instability, CINOTAZ should not be used with solutions containing only sodium bicarbonate.

6.3 Shelf life

24 months.

Reconstituted infusion solution:

Vials containing reconstituted solutions for intravenous use should be stored for not more than 12 hours at room temperature (at or below 25 °C) and not more than 24 hours under refrigeration (2 – 8 °C).

Diluted infusion solutions:

Solutions prepared for intravenous use should be stored for not more than 12 hours at 25 °C and not more than 24 hours at 2 – 8 °C in IV bags or syringes. Unused solution should be discarded.

6.4 Special precautions for storage

Dry powder:

Vials containing sterile dry powder should be stored at controlled room temperature. Store at or below 25 °C.

Keep the vial in the outer carton until required for use.

6.5 Nature and contents of container

CINOTAZ 2: 20 mL clear colourless Type I glass vial with grey bromobutyl rubber stopper, silver aluminium seal and blue flip-off seal.

CINOTAZ 4: 30 mL clear colourless Type I glass vial with grey bromobutyl rubber stopper, silver aluminium seal and white flip-off seal, or

50 mL clear colourless Type I glass vial with grey bromobutyl rubber stopper, silver aluminium seal and yellow flip-off seal.

6.6 Special precautions for disposal and other handling

Reconstitution directions

Diluents for reconstitution:

Sterile water for injection

Bacteriostatic water for injection

Sodium chloride injection.

Each vial of CINOTAZ 2 (2 g / 0,25 g) should be reconstituted with 10 mL of one of the above diluents. Shake until dissolved.

Each vial of CINOTAZ 4 (4 g / 0,5 g) should be reconstituted with 20 mL of one of the above diluents. Shake until dissolved.

For intravenous infusion:

The reconstituted solution may be further diluted to the desired volume (e.g. 50 mL or 100 mL) with one of the reconstitution diluents or with:

Dextrose 5 % in water.

CINOTAZ formulation is compatible with Lactated Ringer's solution.

Co-administration of CINOTAZ with aminoglycosides

Due to *in vitro* inactivation of the aminoglycoside by the beta-lactam antibiotics, CINOTAZ and the aminoglycoside are recommended for separate administration. CINOTAZ and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see section 4.5).

In circumstances where co-administration is preferred, the reformulated CINOTAZ containing EDTA supplied in vials is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Amino-glycoside	**Piperacillin/ tazobactam (grams) dose**	**Piperacillin/ tazobactam diluent volume (mL)**	**Aminoglycoside concentration range (mg/ml)**	**Acceptable diluents**
Amikacin	**2 g/0,25 g** **4 g/0,5 g**	50, 100, 150	1,75 – 7,5	0,9 % sodium chloride or 5 % dextrose
Gentamycin	**2 g/0,25 g** **4 g/0,5 g**	100, 150	0,7 – 3,32	0,9 % sodium chloride

The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening) and renal function (creatinine clearance).

Compatibility of CINOTAZ with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamycin with the dosages of CINOTAZ listed in the above table have been established as compatible for co-administration via the Y-site. Simultaneous co-administration via Y-site in any other manner than listed above may result in inactivation of the aminoglycoside by CINOTAZ.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

8. REGISTRATION NUMBERS

CINOTAZ 2: 45/20.1.1/0399

CINOTAZ 4: 45/20.1.1/0400

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 July 2017

10. DATE OF REVISION OF THE TEXT

04 Feb 2025