Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Piperin 4 g/0.5 g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial or bottle contains 4 g piperacillin (as piperacillin sodium) and 0.5 g tazobactam (as tazobactam sodium).

Excipients with known effect:
Each vial or bottle contains 9.44 mmol (217 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

A white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperin is indicated for the treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

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.

Piperin may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Note: Use for bacteraemia due to extended-beta-lactamase (ESBL) producing E. coli and K. pneumoniae (ceftriaxone non-susceptible), is not recommended in adult patients, see section 5.1.

Children 2 to 12 years of age

- Complicated intra-abdominal infections

Piperin 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

Posology

The dose and frequency of Piperin 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	**Piperin 4 g/0.5 g**
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Patients with 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)	**Piperin (recommended dose)**
>40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 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.

Patients with hepatic impairment
No dose adjustment is necessary (see section 5.2).

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 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam 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.

Patients with 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)	**Piperin (recommended dose)**
>50	No dose adjustment needed.
≤50	70 mg piperacillin / 8.75 mg 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 Piperin 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.

Method of administration

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients listed in section 6.1.

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 Piperin, 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.

Piperacillin/tazobactam may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis (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 Piperin should be discontinued.

Therapy with Piperin 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 haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

This medicinal product contains 217 mg of sodium per each vial or bottle, equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This should be taken into consideration for patients who are 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 haemodialysis patients. Intravenous doses 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 multicentre, 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.
Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH have been reported in patients treated with piperacillin/tazobactam, 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 (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, piperacillin/tazobactam treatment should be discontinued.

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 mechanisms of action, it is expected that the neuromuscular blockade produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Oral anticoagulants
During simultaneous administration of heparin, oral anticoagulants and other substances that may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Methotrexate
Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.

Probenecid
As with other penicillins, concurrent administration of probenecid and piperacillin / tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

Aminoglycosides

Piperacillin, either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.

The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

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

Vancomycin
Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see section 4.4). Some of these studies have reported that the interaction is vancomycin dose-dependent. 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 Piperin 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 Piperin.
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 Piperin 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 Piperin in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactamshould 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 human 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported adverse reaction is diarrhoea (occurring in 1 patient out of 10).

Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-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	**Not known** (cannot be estimated from available data)
Infections and infestations		Candidal superinfection*		Pseudo-membranous colitis	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*,	leukopenia	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, eosinophilia*, thrombocytosis*,
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia,		
Psychiatric disorders		insomnia			delirium*
Nervous system disorders		headache	seizure*		
Vascular disorders			hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, nausea, constipation, dyspepsia		stomatitis	
Hepatobiliary disorders					hepatitis*, jaundice,
Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculopapular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous, purpura
Musculoskeletal and connective tissue disorders			arthralgia, myalgia		
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*

General disorders and administration site conditions		pyrexia, injection site reaction	chills		
Investigations		alanine aminotransferase, increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gammaglutamyltransferase increased

*ADR identified post-marketing

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

Beta-lactam antibiotic class effects
Beta-lactam antibiotics, including piperacillin tazobactam, may lead to manifestations of encephalopathy and convulsions (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Symptoms
There have been post-marketing reports of overdose with piperacillin / tazobactam. The majority of those events experienced, including nausea, vomiting and diarrhoea, have also been reported with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment
In the event of an overdose, piperacillin / tazobactam treatment should be discontinued. No specific antidote is known.

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

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Beta-lactam antibacterials, Penicillins, Combinations of penicillins incl. 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. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / Pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.

Mechanism of resistance
The two main mechanisms of resistance to piperacillin / tazobactam are:

- Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.
- Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.

Additionally, alterations in bacterial membrane permeability, as well as expression of multi-drug efflux pumps, may cause or contribute to bacterial resistance to piperacillin / tazobactam, especially in Gram-negative bacteria.

Breakpoints

EUCAST Clinical MIC Breakpoints for piperacillin / tazobactam (EUCAST Clinical Breakpoint Table Version 12.0, valid from 2022-01-01). For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.

Pathogen	**Species-related breakpoints (S≤/R>), mg/L of piperacillin**
Enterobacterales (formerly *Enterobacteriaceae*)	8/8[1]
Pseudomonas spp.	<0.001/16[1]
Staphylococcus species	-[2,3,4]
Enterococcus species	-[5]
Streptococcus Groups A, B, C, and G[7]	-[6]
Streptococcus pneumoniae [7]	-[8, 12]
Viridans group streptococci[7]	-[9, 10]
Haemophilus influenzae	0.25/0.25[1]
Moraxella catarrhalis	-[11]
Anaerobic bacteria	
Bacteroides spp.	8/8[1]
Prevotella spp.	0.5/0.5[1]
Fusobacterium necrophorum	0.5/0.5[1]
Clostridium perfringens	0.5/0.5[1]
Cutibacterium acnes	0.25/0.25[1]
Achromobacter xylosoxidans	4[1]
Vibrio spp.	1[1]
Non-species related (PK/PD) breakpoints	8/16[1]

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

[2] Most S. aureus are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin.

Isolates that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactam β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Isolates that test resistant to cefoxitin are resistant to all penicillins.

[3] Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in all species of staphylococci but methicillin resistance can be detected with cefoxitin as described.

[4] Ampicillin susceptible S. saprophyticus are mecA -negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[5] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in E. faecalis (confirm with MIC) but common in E. faecium.

[6] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.
[6]

[7] The addition of a beta-lactamase inhibitor does not add clinical benefit.

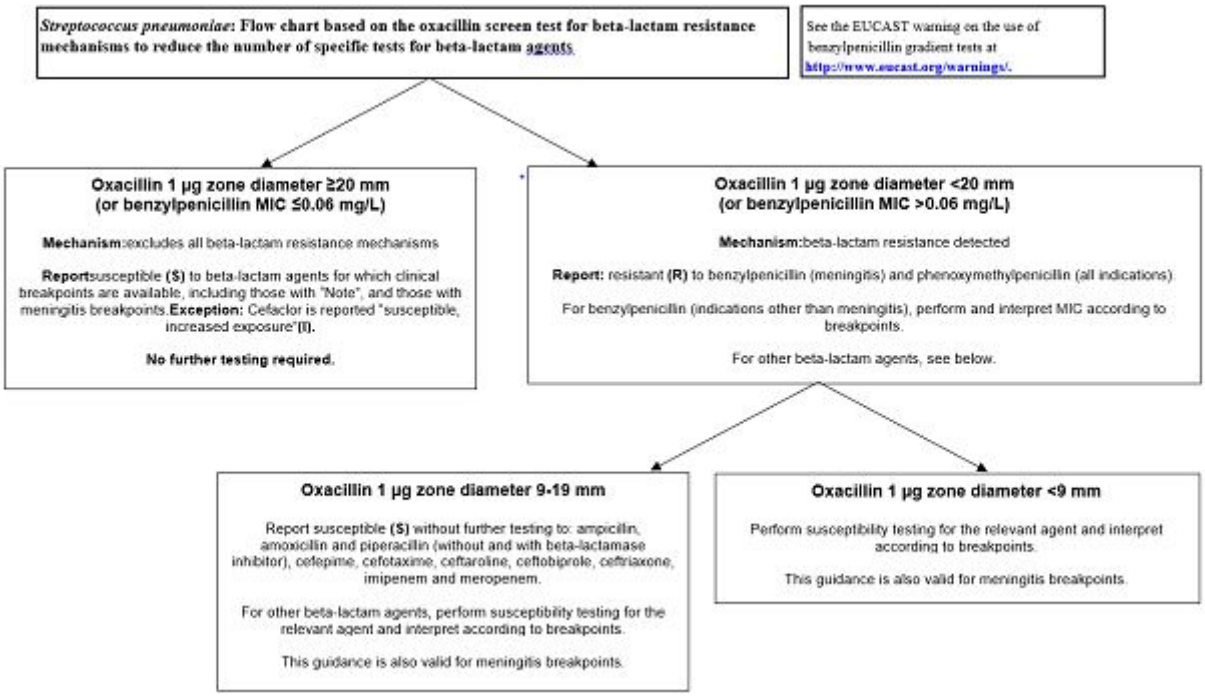
[8] Susceptibility inferred from ampicillin (indications other than meningitis).

[9] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note"). Isolates categorised as screen positive should be tested for susceptibility to individual agents or reported resistant.

[10] For benzylpenicillin screen negative isolates (inhibition zone ≥18 mm or MIC ≤0.25 mg/L), susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates (inhibition zone 0.25 mg/L), susceptibility is inferred from ampicillin.

[11] Susceptibility can be inferred from amoxicillin-clavulanic acid.

[12] The oxacillin 1 µg disk diffusion screening test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone =20 mm, or benzylpenicillin MIC =0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). When the screen is positive (oxacillin zone <20 mm, or benzylpenicillin MIC >0.06 mg/L), **See flow chart below**.



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
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* (ampicillin- or penicillin-susceptible isolates only) *Listeria monocytogenes* *Staphylococcus aureus* (methicillin-susceptible isolates only) *Staphylococcus species, coagulase negative* (methicillin-susceptible isolates only) *Streptococcus agalactiae* (Group B streptococci)† *Streptococcus pyogenes* (Group A streptococci)†
Aerobic Gram-negative micro-organisms *Citrobacter koseri* *Haemophilus influenzae* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobic Gram-positive micro-organisms *Clostridium species* *Eubacterium species* *Anaerobic gram-positive cocci*††
Anaerobic Gram-negative micro-organisms *Bacteroides fragilis* group *Fusobacterium* species *Porphyromonas* species *Prevotella* species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecium* *Streptococcus pneumoniae*† *Streptococcus viridans group*† Aerobic Gram-negative micro-organisms *Acinetobacter baumannii* *Citrobacter freundii* *Enterobacter species*

Escherichia coli *Klebsiella pneumoniae* 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 *Burkholderia cepacia* *Legionella species* *Ochrobactrum anthropi* *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Mycoplasma pneumoniae*
† Streptococci are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in penicillin-binding proteins (PBPs) and, therefore, susceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in S. pyogenes. †† Including Anaerococcus, Finegoldia, Parvimonas, Peptoniphilus, and Peptostreptococcus spp.

Merino Trial (blood stream infections due to ESBL producers)

In a prospective, non-inferiority, parallel-group, published randomized clinical trial, definitive (i.e. based on susceptibility confirmed in-vitro) treatment with piperacillin / tazobactam, compared with meropenem, did not result in a non-inferior 30-day mortality in adult patients with ceftriaxone-non-susceptible E. coli or K. pneumoniae blood stream infections.

A total of 23 of 187 patients (12.3%) randomized to piperacillin / tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI − ∞ to 14.5%]; P = 0.90 for non-inferiority). The difference did not meet the non-inferiority margin of 5%.

Effects were consistent in an analysis of the per-protocol population, with 18 of 170 patients (10.6%) meeting the primary outcome in a piperacillin / tazobactam group compared with 7 of 186 (3.8%) in the meropenem group (risk difference, 6.8% [one-sided 97.5% CI, - ∞ to 12.8%]; P = 0.76 for non-inferiority).

Clinical and microbiological resolution (secondary outcomes) by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin / tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, 6.2% [95% CI − 15.5 to 3.1%]; P = 0.19). For secondary outcomes, statistical tests were 2-sided, with a P <0.05 considered significant.

In this trial, a mortality imbalance between study groups was found. It was supposed that deaths occurred in piperacillin / tazobactam group were related to underlying diseases rather than to the concomitant infection.

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 tissues 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 that has been found to be micro-biologically inactive.

Elimination

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

Piperacillin is excreted rapidly as unchanged substance, 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 substance 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 slightly 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

Non-clinical 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 stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administrationof tazobactam or the combination piperacillin / tazobactam in the rat.

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 in section 6.6.

This product must not be mixed or co-administrated with any aminoglycoside. The mixing of beta-lactam antibiotics 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.

Piperacillin / tazobactam should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Due to chemical instability, piperacillin / tazobactam should not be used in solutions containing only sodium bicarbonate.

Lactated Ringer's (Hartmann's) solution is not compatible with piperacillin / tazobactam.

Piperacillin / tazobactam should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Unopened:
2 years

After reconstitution (and dilution):
Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C and for 48 hours at 2-8°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/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials:
This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml bottle glass type II, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.
50 ml bottle glass type II, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.
Pack sizes of 1, 5, 10, 12 and 50 bottles.

50 ml injection vial glass type III, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.
50 ml injection vial glass type II, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap
Pack sizes of 1, 5, 10, 12 and 50 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Intravenous use
Reconstitute each vial/bottle with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 3 minutes (for details on handling, please see below).

Content of vial/bottle	Volume of solvent* to be added to vial/bottle
2 g/0.25 g (2 g piperacillin and 0.25 g tazobactam)	10 ml
4 g/0.5 g (4 g piperacillin and 0.5 g tazobactam)	20 ml

* Compatible solvents for reconstitution:

- water for injection;
- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in sodium chloride 9 mg/ml (0.9%) solution.

The reconstituted solutions should be withdrawn from the vial/bottle by syringe. When reconstituted as directed, the vial/bottle contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in water for injection;
- dextran (grade 40) 60 mg/ml (6%) solution in sodium chloride 9 mg/ml (0.9%) solution.

Co-administration with aminoglycosides
Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Piperin and the aminoglycoside are recommended for separate administration. Piperin and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.
In circumstances where co-administration is recommended, Piperin is compatible for simultaneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Piperacillin/Tazobactum Dose	Piperacillin/Tazobactum 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% glucose
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

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

Compatibility of piperacillin/tazobactum with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dose of piperacillin/tazobactum listed in the above table have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site in any manner other than listed above may result in inactivation of the aminoglycoside by Piperacillin/tazobactum.

See section 6.2 for incompatibilities.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/113/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th October 2008

Date of last renewal: 22nd June 2013

10 DATE OF REVISION OF THE TEXT

July 2023