SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam - Fresenius 2 g/0.25 g.
Piperacillin/Tazobactam - Fresenius 4 g/0.5 g.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Piperacillin/Tazobactam - Fresenius 2 g/0.25 g: Each vial contains 2 g of piperacillin (as sodium salt) and 0.25 g of tazobactam (as sodium salt). One vial of powder for solution for infusion contains 4.9 mmol (112 mg) of sodium.

Piperacillin/Tazobactam - Fresenius 4 g/0.5 g: Each vial contains 4 g of piperacillin (as sodium salt) and 0.5 g of tazobactam (as sodium salt). One vial of powder for solution for infusion contains 9.7 mmol (224 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/Tazobactam is indicated for the treatment of systemic and/or local infections caused by susceptible organisms.

Piperacillin/Tazobactam in combination with an aminoglycoside is indicated for the treatment of suspected bacterial infections in neutropenic adults and children above 2 years.
Appendicitis complicated by rupture with peritonitis and/or abscess formation in children aged 2-12 years.

Piperacillin/Tazobactam is indicated for the treatment of the following infections in 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)

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

Appropriate culture and susceptibility tests should be performed treatment in order to identify organisms causing infections and to determine their susceptibilities to Piperacillin/Tazobactam. Because of its broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic organisms as listed above, Piperacillin/Tazobactam is particularly useful in the

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

Therapy with Piperacillin/Tazobactam may, however, be initiated before results of such tests are known. Modification of the treatment may be required once these results become available or if there is no clinical response.

In serious infections presumptive therapy with Piperacillin/Tazobactam may be initiated before susceptibility test results are available.

Piperacillin/Tazobactam acts synergistically with aminoglycosides against certain strains of Pseudomonas aeruginosa. Combined therapy has been successful, especially in patients with impaired host defenses. Both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility test become available, antimicrobial therapy should be adjusted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin/Tazobactam - Fresenius and other antibacterial drugs, Piperacillin/Tazobactam – Fresenius should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration

Posology

Piperacillin/Tazobactam – Fresenius should be administered by intravenous infusion over 30 minutes. Neutropenic patients with signs of infection (e.g. fever) should receive immediate empirical antibiotic therapy before results are available.

Adults and adolescents (over 12 years)

The usual dosage for adults and juveniles with normal renal function is 4 g piperacillin/ 0.5 g tazobactam given every eight hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin/ 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

Nosocomial pneumonia

Initial presumptive treatment of patients with nosocomial pneumonia should start with Piperacillin/Tazobactam – Fresenius at a dosage of 4 g piperacillin/ 0.5 g tazobactam every six hours plus an aminoglycoside, totaling 18.0 g (16.0 g piperacillin/ 2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients from whom Pseudomonas aeruginosa is isolated. If Pseudomonas aeruginosa is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Due to the in vitro inactivation of the aminoglycoside by beta-lactam antibiotics, Piperacillin/Tazobactam – Fresenius and the aminoglycoside are recommended for separate administration. Piperacillin/Tazobactam – Fresenius and the aminoglycoside should be reconstituted, diluted and administered separately when concomitant therapy with aminoglycosides is indicated. (See interaction, section 4.5).

The dose and frequency of Piperacillin/Tazobactam depends on the severity and localization of the infection and expected pathogens.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Table 1	
Treatment frequency	**Piperacillin/Tazobactam 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)

Renal Insufficiency: Adults

In patients with renal insufficiency (Creatinine clearance $\leq$ 40 ml/min), the intravenous dose of Piperacillin/Tazobactam – Fresenius should be adjusted to the degree of actual renal function impairment and each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly.

In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Piperacillin/Tazobactam – Fresenius for patients with renal insufficiency are as follows:

Recommended dosing of Piperacillin/Tazobactam – Fresenius in patients with normal renal function and renal insufficiency:

(As total grams Piperacillin/Tazobactam)

Table 2		
Renal function (Creatinine clearance (ml/min))	**All indications (except nosocomial pneumonia)**	**Nosocomial pneumonia**
> 40 ml/min	No dose adjustment necessary	4.5 q 6 h
20-40 ml/min*	Maximum dose suggested: 4.5 g q 8 h	3.375 q 6 h
< 20 ml/min*	Maximum dose suggested: 4.5 g q 12 h	2.25 q 6 h
Hemodialysis**	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h

* Creatinine clearance for patients not receiving hemodialysis

** 0.75 g should be administered following each hemodialysis session on hemodialysis days

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia.

Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g Piperacillin/Tazobactam – Fresenius should be administered following each dialysis period on

hemodialysis days. No additional dosage of Piperacillin/Tazobactam – Fresenius is necessary for CAPD patients.

Duration of Therapy

The usual duration of Piperacillin/Tazobactam – Fresenius treatment for most indications is in the range of 5-14 days. However, the recommended duration of Piperacillin/Tazobactam – Fresenius treatment of nosocomial pneumonia is 7 to 14 days.

In all conditions, the duration of treatment should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Patients with hepatic impairment

Dosage adjustment of Piperacillin/Tazobactam – Fresenius is not warranted in patients with hepatic cirrhosis (see section 5.2 Pharmacokinetic properties).

Elderly patients

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

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

One vial of Piperacillin/Tazobactam – Fresenius 2 g/0.25 g contains 4.9 mmol (112 mg) of sodium and one vial of Piperacillin/Tazobactam – Fresenius 4 g/0. 5 g contains 9.7 mmol (224 mg) of sodium.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

This drug is known to be substantially excreted by the kidney, and the risk of the toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric patients (2-12 years of age)

For children with appendicitis older than 2 years and/or peritonitis, weighing up to 40 kg, and with normal renal function, the recommended Piperacillin/Tazobactam – Fresenius dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram of body weight, every 8 hours. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose.

The following table summarizes the treatment frequency and the dose per body weight for pediatric patients 2-12 years of age by indication or condition:

Table 3

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.

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):

Table 4	
Creatinine clearance (ml/min)	**Piperacillin/Tazobactam (recommended dose)**
> 50	No dose adjustment needed
≤ 50	70 mg piperacillin/ 8.75 mg tazobactam/ kg every 8 hours

For children on hemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam / kg should be administered following each dialysis period.

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.

Method of Administration

Piperacillin/Tazobactam – Fresenius 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).

Piperacillin/Tazobactam – Fresenius 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

Precautions to be taken before handling or administering the medicinal product

For instructions on reconstitution/dilution 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.

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.

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 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 haematopoietic function 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.

Each vial of Piperacillin/Tazobactam 2 g / 0.25 g contains 4.9 mmol (112 mg) of sodium and Piperacillin/Tazobactam 4 g / 0.5 g contains 9.7 mmol (224 mg) of sodium. 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 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.

Combined use of piperacillin /tazobactam and vancomycin may be associated with an increased incidence of acute Kidney injury (see section 4.5)

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.

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 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 and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported.

Positive test results for the assays listed above in patients receiving Piperacillin/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 (see section 5.3).

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.

Breastfeeding

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 effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported adverse reactions 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)	**Frequency not known (cannot be estimated from available data)**
Infections and infestations		candida infection *		pseudo-membranous colitis	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*	leukopenia	agranulocytosis	Pancytopenia*, neutropenia, haemolytic anaemia*, eosinophilia*, thrombocytosis*
Immune system disorders					anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia		
Psychiatric disorders		insomnia			delirium*
Nervous system disorders		headache	seizure*		
Vascular disorders			hypotension, thrombophlebitis, phlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia

Gastrointestinal disorders	diarrhea	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	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gamma-glutamyltransferase increased

		thromboplastin time prolonged			

*ADR identified post marketing
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Beta -lactam antibiotics 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
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by following this link: https://sideeffects.health.gov.il, and by emailing the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

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, 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. 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 for Piperacillin / Tazobactam (EUCAST Clinical Breakpoint Table 10.0, valid from 2020-01-01)
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)	8/16
Pseudomonas *aeruginosa*	<0.001/16 [1]
Staphylococcus species	-2
Enterococcus species	-3
Streptococcus Groups A,B,C,and G	-4
Sreptococcus pneumoniae	-5
Viridans group streptococci	-6

Haemophilus influenza	0.25/0.25
Moraxella catarrhalis	-[7]
Gram -positive anaerobes (except *Clostridioides difficile*)	8/16
Gram -negative anaerobes	8/16
Non-species related (PK/PD) breakpoints	4/16

[1] For several agents, EUCAST has introduced breakpoints which categorise wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)". Susceptible breakpoints for these organism-agent combinations are listed as arbitrary, "off scale" breakpoints of S ≤ 0.001 mg/L.
[2] Most staphylococci are penicillinase producers, and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to 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. Staphylococci that test resistant to cefoxitin are resistant to all penicillins. Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).
[3] 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*.
[4] The susceptibility of *Streptococcus* groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for *Streptococcus* group B. *Streptococcus* groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.
[5] The oxacillin 1 μg disk screen 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). *Streptococcus pneumoniae* do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit. Susceptibility inferred from ampicillin (MIC or zone diameter).
[6] For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.
[7] Susceptibility can be inferred from amoxicillin-clavulanic acid.

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 (Goup B streptococci) †
Streptococcus pyogenes (GoupA streptococci) †
Aerobic Gram-negative micro-organisms
Citrobacter koseri
Haemophilus influenza
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 pneumonia †
Streptococcus viridans group †
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
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
Burkholderia cepacian
Legionella species
Ochrobactrum anthropi
Stenotrophomonas maltophilia
Other microorganisms

Chlamydophilia pneumonia
Mycoplasma pneumonia
[$] Species showing natural intermediate susceptibility. [†] 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.

5.2 Pharmacokineticproperties

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 microbiologically 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 administration of 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.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Piperacillin/tazobactam should not be mixed with other drugs 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 that contain 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

The expiry date of the product is indicated on the packaging materials.

Reconstituted/diluted Pipercillin/Tazobatam: Chemical and physical in use stability has been demonstrated for 24 hours at 2-8 °C.

From the microbiological point of view, 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 to 8° C, unless reconstitution/dilution has be taken place in controlled and validated conditions.

Unused solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after reconstitution/dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Piperacillin/Tazobactam - Fresenius 2 g/0.25 g:
Colourless glass vial (type II) of 15 ml closed with a halobutyl rubber stopper
Pack sizes: 1, 5 and 10 vials.
Colourless glass vial (type II) of 50 ml closed with a halobutyl rubber stopper Pack sizes: 1, 5 and 10 vials.

Piperacillin/Tazobactam - Fresenius 4 g/0.5 g:
Colourless glass vial (type II) of 50 ml closed with a halobutyl rubber stopper
Pack sizes: 1, 5 and 10 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Shake until dissolved. When shaken constantly,

reconstitution generally occurs within 5 to 10 minutes (for details on handling, please see below).

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

* Compatible solvents for reconstitution:

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections (1)

(1) Maximum recommended volume of sterile water for injection per dose is 50 ml.

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial 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:

- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Dextran 6% in 0.9% sodium chloride

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 MANUFACTURER

Labesfal - Laboratorios Almiro S.A, Fresenius Kabi Group, Portugal
Lagedo, Santiago De Besteiros, 3465 - 157, Portugal

8 REGISTRATION HOLDER

Neopharm (Israel) 1996 LTD. Hashiloach 6, POB 7063 Petach Tiqva 4917001

9 REGISTRATION NUMBER(S)

Piperacillin/Tazobactam - Fresenius 2 g/0.25 g: 151-27-33273
Piperacillin/Tazobactam - Fresenius 4 g/0.5 g: 151-28-33274

Revised in January 2022 according to MOHs guidelines