1. NAME OF THE MEDICINAL PRODUCT

Tazo-Pip Avenir 4.5 g

Powder for Solution for Injection or Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

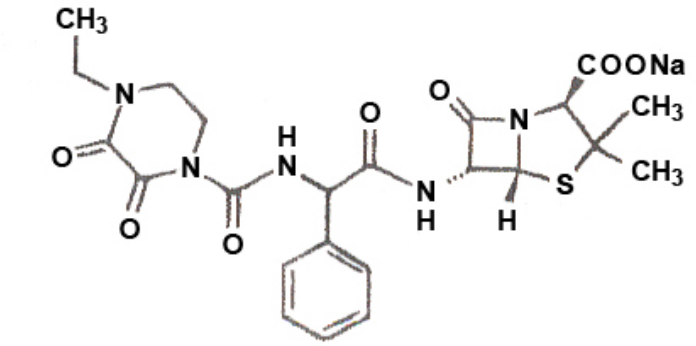
One vial of powder for solution for injection or infusion contains 9.44 mmol (217 mg) of sodium.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

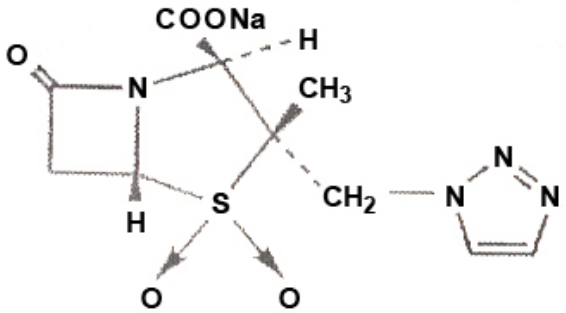
White to off white powder.

Tazo-Pip Avenir 4.5g (Piperacillin/Tazobactam for Injection) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.
Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (*2*S,*5*R,*6*R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5Na0_7S$ and the molecular weight is 539.5. The chemical structure of piperacillin sodium is:



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-methyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-
carboxylic acid 4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4Na0_5S$ and the molecular weight is 322.3.

The chemical structure of tazobactam sodium is:



4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antibiotic for the treatment of moderate to severe systemic and/or local bacterial 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.
Appendicitis complicated by rupture with peritonitis and/or abscess formation in children aged 2-12 years.

This indication of the medicine has not been evaluated in pediatric patients under two years.

Appropriate culture and susceptibility tests should be performed before 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, 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 test 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.

4.2 Posology and method of administration

Posology

The dose and frequency of piperacillin/tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

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

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

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

Treatment frequency	**Piperacillin/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 impairment
The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	**Piperacillin/tazobactam (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, 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 should be administered following each dialysis period on hemodialysis days.

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections

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

Dose per weight and treatment 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):

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

Use in children aged below 2 years

The safety and efficacy of piperacillin/tazobactam in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days…. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Route of administration
Piperacillin/tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For reconstitution instructions, see section 6.6.

4.3 Contraindications

Hypersensitivity to piperacillin or any of the beta-lactam antibiotics and to tazobactam or any other beta-lactamase inhibitor.

4.4 Special warnings and precautions for use

Warnings

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 Tazo-Pip Avenir 4.5g, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta lactam agents (e.g.cephalosporins,monobactam or carbapenem) and other allergens.

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins including piperacillin/tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens.
Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

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

Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases piperacillin/tazobactam, should be discontinued.

Precautions

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

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 β-lactam antibiotics. 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 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 (a full blood count) should be performed.

Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

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

This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for injection or infusion. 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 who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

Modest elevation of indices of liver function may be observed.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients (see also 4.8).

Until further experience is available, Tazo-Pip Avenir 4.5g should not be used in children who do not have neutropenia.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with probenecid:

Concurrent administration of probenecid and piperacillin/tazobactam produced a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of either drug are unaffected.

Interaction with antibiotics:

No clinically relevant adverse pharmacokinetic interaction with tobramycin or vancomycin has been observed in healthy adults with a normal renal function. The clearance of tobramycin and gentamicin was enhanced in patients with severe renal dysfunction using piperacillin/tazobactam. In these patients mixing of piperacillin/tazobactam formulation with tobramycin and gentamicin was excluded.

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

Interaction with anticoagulants:

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

Interaction with vecuronium:

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-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. This should be taken into account when piperacillin/tazobactam is used peri-operatively.

Interaction with methotrexate:

Piperacillin may reduce the excretion of methotrexate. Serum levels of methotrexate should be monitored in patients on methotrexate therapy.

Interaction with laboratory test results:The administration of piperacillin/tazobactam 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 reaction be used.

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.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving piperacillin-tazobactam 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. Therefore, positive test results in patients receiving piperacillin-tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies with piperacillin/tazobactam in combination or with piperacillin or tazobactam alone in pregnant women. Studies in animals have shown reproductive toxicity (see 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.

Piperacillin is excreted in low concentrations in breast milk Tazobactam concentrations in human milk have not been studied. The effect on the suckling infant is unknown. Women who are breast-feeding should be treated only if clearly indicated. Diarrhoea and fungal infections of the mucous membranes as well as sensitisation could occur in the breast-fed infant.

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. However, side effects may occur (see also 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed by frequency as follows: Very common ($\geq$ 1/10); common ($\geq$ 1/100 to <1/10); uncommon ($\geq$ 1/1 000 to $\leq$ 1/100); rare ($\geq$ 1/10 000 to $\leq$ 1/1 000); very rare ($\leq$ 1/10 000); not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are diarrhoea, nausea, vomiting, and rash, each having a frequency of $\geq$ 1% but $\leq$ 10%.

Body System	**Frequency**	**Adverse Reaction**
Infections and infestations	Uncommon	Candidal superinfection
Blood and lymphatic system disorders	Uncommon	Leucopenia, neutropenia, thrombocytopenia
	Rare	Anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged,

		eosinophilia
	Very rare	Agranulocytosis, Coombs' direct test positive, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, thrombocythaemia
Immune system disorders	Uncommon	Hypersensitivity reaction
	Rare	Anaphylactic/anaphylactoid reaction (including shock)
Metabolism and nutritional disorders	Very rare	Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia
Nervous system disorders	Uncommon	Headache, insomnia
Vascular disorders	Uncommon	Hypotension, phlebitis, thrombophlebitis
	Rare	Flushing
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomiting
	Uncommon	Constipation, dyspepsia, jaundice, stomatitis
	Rare	Abdominal pain, pseudomembranous colitis, ~~dry mouth~~
Hepatobiliary disorders	Uncommon	Alanine aminotransferase increased, aspartate aminotransferase increased
	Rare	Blood bilirubin increased, blood alkaline phosphatase increased, gamma glutamyltransferase increased, hepatitis
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash
	Uncommon	Pruritus, urticaria
	Rare	Bullous dermatitis, erythema multiforme, exanthema
	Very rare	Stevens-Johnson Syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, myalgia
Renal and urinary disorders	Uncommon	Blood creatinine increased
	Rare	Tublointerstitial nephritis, renal failure
	Very rare	Blood urea increased

General disorders and administration site conditions	Uncommon	Pyrexia, injection site reaction
	Rare	Chills

The administration of high doses of beta-lactams, particularly in patients with renal insufficiency, can lead to encephalopathies (consciousness fluctuation, myoclonus and convulsions).
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

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

Treatment of Intoxication

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. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

Excessive serum concentrations of either piperacillin or tazobactam will be reduced by haemodialysis (for more details see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, including beta-lactamase inhibitors.

ATC Classification: J01CR05

Mechanism of action:

Piperacillin, a broad spectrum, semisynthetic 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 a potent 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.

Mechanism of resistance:

The presence of tazobactam expands the spectrum of activity of piperacillin to include microorganisms that would otherwise, due to the formation of beta-lactamase, be resistant to piperacillin and other beta-lactam antibiotics. *In vitro* investigation has demonstrated that the type I beta-lactamase inducing ability of tazobactam is insignificant with regard to Gram-negative bacteria. *In vitro* studies have demonstrated a synergetic effect of Piperacillin/Tazobactam and aminoglycosides against *Pseudomonas aeruginosa* and other bacteria, including beta-lactamase producing strains.

Breakpoints

The minimum inhibitory concentration (MIC) breakpoints separating susceptible, intermediately susceptible and resistant organisms have been defined as follows:

EUCAST clinical MIC breakpoints 2008 (version 1.2):

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 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.

Commonly susceptible species

Gram positive aerobes

Brevibacterium spp

Enterococcus faecalis

Listeria monocytogenes

Staphylococcus spp. methicillin-sensitive

Streptococcus pneumoniae

Streptococcus pyogenes

Group B *streptococci*

Streptococcus spp*

Gram negative aerobes

Branhamella catarrhalis

Citrobacter koseri

*Haemophilus influenzae**

Haemophilus spp.

Proteus mirabilis

Salmonella spp.

Shigella spp.

Gram positive anaerobes

Clostridium spp.

Eubacterium spp.

Peptococcus spp.

Peptostreptococcus spp.

Gram negative anaerobes

*Bacteroides fragilis**

Bacteroides fragilis group

Fusobacterium spp.

Porphyromonas spp.

Prevotella spp*

Species for which resistance may be a problem

Gram positive aerobes

Staphylococcus aureus, methicillin-sensitive

Staphylococcus epidermis, methicillin-sensitive

Enterococcus avium ($)

Enterococcus faecium (+ $)

Propionibacterium acnes ($)

Viridans streptococci

Gram negative aerobes

Actinobacter spp (+ $)

Burkholderia cepacia

Citrobacter freundii

Enterobacter spp.

*Escherichia coli **

Klebsiella spp.

Proteus, indole positive

*Pseudomonas aeruginosa**

*Pseudomonas spp. **

Pseudomonas stutzeri $

Serratia spp.

Gram negative anaerobes

Bacteroides spp. *

Inherently resistant organisms

Gram positive aerobes

Corynebacterium jeikeium
Staphylococcus spp. methicillin resistant

Gram negative aerobes
Legionella spp

Stenotrophomonas maltophilia +$

* Clinical effectiveness against this has been demonstrated in the registered indications.

($) 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.

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.

There is a greater proportional (approximately 28%) increase in plasma levels of piperacillin and tazobactam with increasing dose over the dosage range of piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg.

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 is 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 micro-biologically inactive.

Elimination

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

Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of Piperacillin/Tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to reduce the rate of elimination of tazobactam.

Impaired Renal Function

Piperacillin and tazobactam are haemodialysable: 31% (piperacillin) and 39% (tazobactam) of administered doses are filtrated. During peritoneal dialysis, 5% of administered piperacillin and 12% of administered tazobactam are found in the dialysis liquid. Patients treated by chronic ambulatory peritoneal dialysis should receive the same dose as non dialysed patients with severe renal insufficiency.

Impaired Liver Function

Plasma concentrations of piperacillin and tazobactam are prolonged in hepatically impaired patients. The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustments in patients with hepatic impairment are not necessary.

Paediatric patients

The pharmacokinetics of Piperacillin/Tazobactam has been studied in paediatric patients with intra-abdominal infections and other kinds of infections. In every age group, renal fraction of elimination of piperacillin and tazobactam was approximately 70% and 80%, respectively, like in adults.

Mean pharmacokinetic parameters of Piperacillin/Tazobactam of paediatric patients of different age groups.

Piperacillin			Tazobactam	
Age group	Half-life	Clearance (ml/min/kg)	Half-life	Clearance (ml/min/kg)
2-5 years	0.7	5.5	0.8	5.5
6-12 years	0.7	5.9	0.9	6.2

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with piperacillin/tazobactam.

A fertility study of piperacillin/tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs following i.p. administration to rats. Fertility of the F1 generation and embryonic development of the F2 generation was not impaired. A teratogenicity study in rats, did not show teratogenic effects after i.v. administration. In the rat, effects on the embryonic development were observed at maternal toxic doses. Peri/postnatal development was impaired (reduced fetal weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after i.p. administration in the rat.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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.

Tazo-Pip Avenir 4.5g should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Tazo-Pip Avenir 4.5g should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Because of chemical instability, Tazo-Pip Avenir 4.5g should not be used with solutions containing only sodium bicarbonate.

Lactated Ringer's solution is not compatible with Tazo-Pip Avenir 4.5g.

Tazo-Pip Avenir 4.5g should not be added to blood products or albumin hydrolysates

6.3 Shelf life

Unopened - 3 years

When Tazo-Pip Avenir 4.5g is reconstituted with water for injections or saline, reconstituted solutions will remain stable for 24 hours at 25°C and for 48 hours under refrigeration 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 has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Store at room temperature up to 25°C.

After reconstitution: Store at 2-8^{o}C (see 6.3 Shelf Life).

6.5 Nature and contents of container

Packs of one Type II glass vial with butyl rubber stopper and aluminium/plastic seal

6.6 Special precautions for disposal and other handling

Intravenous Injection

Each vial of Tazo-Pip Avenir 4.5g Powder for Solution for Injection or Infusion should be reconstituted with 20ml of one of the following diluents:

• Sterile water for injections

• 0.9% sodium chloride for injection

Swirl until dissolved. Intravenous injection should be given over at least three to five minutes.

Intravenous Infusion

Each vial of Tazo-Pip Avenir 4.5g Powder for Solution for Injection or Infusion should be reconstituted with 20ml of Sterile water for injection or 0.9% sodium chloride for injection.

The reconstituted solution should be further diluted to at least 50ml with one of the reconstitution diluents, or with Dextrose 5% in Water or Dextrose 5% in saline or Dextrose 6% in saline.

Displacement Volume

Each gram of Tazo-Pip Avenir 4.5g Powder for Solution for Injection or Infusion has a displacement volume of 0.7ml.

Tazo-Pip Avenir 4.5g Powder for Solution for Injection or Infusion will displace 3.15ml.

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

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

7. MANUFACTURER

Laboratory Reige Jofre, Spain.

8. LICENSE HOLDER

BioAvenir Ltd.,

Kibutz Glil-Yam 46905

9. Registration Number

146 -80 -33342 -00

The format of this leaflet was determined by the Ministry of Health and the content thereof was checked and approved in 07.2014