เอกสารกำกับยาภาษาอังกฤษ

(เหมือนกันทุกขนาดบรรจุ)

1. NAME OF THE MEDICINAL PRODUCT

TAZOPET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

After reconstitution with 20 ml diluent the solution contains piperacillin 200 mg/ml and tazobactam 25 mg/ml.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
Off-white to white cake or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAZOPET is indicated for the treatment of the following systemic and/or local bacterial infections in which beta-lactamase producing bacteria are suspected or have been detected, such as:

Adults/adolescents and the Elderly
- Lower respiratory tract infection;
- Uncomplicated and complicated urinary tract infections (including pyelonephritis);
- Intra-abdominal infections;
- Gynecological infections including endometritis and pelvic inflamatoy disease;
- Skin and soft tissue infection;
- Bacterial septicaemia;
- Bacterial infections in neutropenic adults in combination with an aminoglycoside;

Children (2 to 12 years)
TAZOPET in combination with an aminoglycoside is indicated for Bacterial infections in neutropenic children.

In hospitalised children, **TAZOPET** is indicated for the treatment of intra-abdominal infections including appendicitis and peritonitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
TAZOPET may be given by slow intravenous injection (over at least 3 to 5 minutes) or by slow intravenous infusion (over 20 to 30 minutes).
For reconstitution instructions, see section 6.6.

The treatment of mixed infections caused by piperacillin susceptible organisms and betalactamase producing organisms susceptible to piperacillin/tazobactam generally does not require the addition of another antibiotic.

In patients with nosocomial pneumonia and infections in neutropenic patients piperacillin/tazobactam can be used with an aminoglycoside. If the use of an aminoglycoside is needed, with piperacillin/tazobactam, both piperacillin/tazobactam and the aminoglycoside must be used in full therapeutic doses.

Neutropenic patients with signs of infection (e.g. fever) should receive immediate empirical antibiotic therapy before laboratory results are available.

Adults and children over 12 years each with normal renal function
The usual dosage for adults and children over 12 years is piperacillin/tazobactam 4000/500 mg given every 8 hours.
The total daily dose of piperacillin/tazobactam depends on the severity and localisation of the infection and can vary from piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg administered every 6 or 8 hours.
In neutropenia the recommended dose is piperacillin/tazobactam 4000/500 mg given every 6 hours in combination with an aminoglycoside.

Elderly with normal renal function
Piperacillin/tazobactam may be used at the same dose levels as adults except in cases of renal impairment (see below):

Renal Insufficiency in Adults, the Elderly and Children (over 40 kg) Receiving the Adult Dose
In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

Creatinine clearance (ml/min)	**Recommended Piperacillin/Tazobactam dosage**	
	Total	**Divided doses**
20 – 80	12/1.5g /day	4000/500 mg q 8H
< 20	8/1g /day	4000/500 mg q 12H

For patients on haemodialysis, the maximum daily dose is piperacillin/tazobactam 8/1 g. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of piperacillin/tazobactam 2000/250 mg should be administered following each dialysis period.

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

Children aged 2 - 12 years with normal renal function
Piperacillin/tazobactam is only recommended for the treatment of children with neutropenia.

Neutropenia
For children with normal renal function the dose should be adjusted to 90 mg/kg (piperacillin/tazobactam 80/10 mg), administered every 6 hours, in combination with an aminoglycoside, not exceeding piperacillin/tazobactam 4000/500 mg every 6 hours.

Renal Insufficiency in Children Aged 2-12 Years (or bodyweight less than 40 kg)
In children with renal insufficiency the intravenous dosage should be adjusted to the degree of actual renal impairment as follows:

Creatinine clearance (ml/min)	**Recommended piperacillin/tazobactam dosage**	**Frequency**	**Maximum daily dosage**
> 50	112.5 mg/kg (100 mg piperacillin/ 12.5 mg tazobactam)	q 8H	12/1.5g /day
≤ 50	78.75 mg/kg (70 mg piperacillin/ 8.75 mg tazobactam)	q 8H	8.4/1.05g /day

For children weighing < 50 kg on haemodialysis the recommended dose is 45 mg (piperacillin/tazobactam 40/5 mg) /kg every 8 hours.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Children under 2 years
Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

Hepatic Impairment
No dose adjustment is necessary.

Duration of Therapy
The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.
In acute infections, treatment with Piperacillin/Tazobactam should be continued for 48 hours beyond the resolution of clinical symptoms or the fever.

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.

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.

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 **TAZOPET** contains 8.45 – 10.33 mEq (equivalent to 194.28 – 237.46 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 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 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.

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 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.

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 pseudomembranous 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.

The following 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.
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)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
Common: Candida infection*
Rare: Pseudo-membranous colitis

Blood and lymphatic system disorders
Common: Thrombocytopenia, anaemia*
Uncommon: Leukopenia
Rare: Agranulocytosis
Not known: Pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*, eosinophilia*

Immune system disorders
Not known: Anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*

Metabolism and nutrition disorders
Uncommon: Hypokalaemia

Psychiatric disorders
Common: Insomnia
Not known: Delirium*

Nervous system disorders
Common: Headache
Uncommon: Seizure*

Vascular disorders
Uncommon: Hypotension, thrombophlebitis, phlebitis, flushing

Respiratory, thoracic and mediastinal disorders

Rare: Epistaxis
Not known: Eosinophilic pneumonia

Gastrointestinal disorders
Very common: Diarrhoea
Common Abdominal pain, vomiting, nausea, constipation, dyspepsia
Rare: Stomatitis

Hepatobiliary disorders
Not known: Hepatitis*, jaundice

Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Erythema multiforme*, urticarial, rash maculopapular*
Rare: Toxic epidermal necrolysis*
Not known: 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
Uncommon: Arthralgia, myalgia

Renal and urinary disorders
Not known: Renal failure, tubulointerstitial nephritis*

Investigations
Common: 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
Uncommon: Blood glucose decreased, blood bilirubin increased, prothrombin time prolonged
Not known: Bleeding time prolonged, gamma-glutamyltransferase increased

General disorders and administration site conditions
Common: Pyrexia, injection-site reaction
Uncommon: Chills

*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 effect
Beta-lactam antibiotics, including piperacillin tazobactam, may led to manifestations of encephalopathy and convulsions.

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: Combinations of penicillins, including beta-lactamase inhibitors
ATC classification: J01CR05.

Mechanism of action
Piperacillin, a broad spectrum, semi-synthetic penicillin active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulphone, is 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 micro-organisms 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

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.

Commonly susceptible species

Aerobes, Gram positive:
Brevibacterium spp.
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus spp. methicillin-sensitive
Streptococcus pneumoniae
Streptococcus pyogenes
Group B streptococci
Streptococcus spp.*

Aerobes, Gram negative:
Citrobacter koseri
*Haemophilus influenzae**
Haemophilus spp.
Moraxella catarrhalis
Proteus mirabilis
Salmonella spp.
Shigella spp.

Anaerobes, Gram positive:
Clostridium spp.
Eubacterium spp.
Peptococcus spp.
Peptostreptococcus spp.

Anaerobes, Gram negative:
Bacteroides fragilis *
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp. *

Species for which resistance may be a problem

Aerobes, Gram positive:
Staphylococcus aureus, methicillin-sensitive
Staphylococcus epidermidis, methicillin-sensitive
Enterococcus avium $
Enterococcus faecium +$
Propionibacterium acnes $
Viridans streptococci

Aerobes, Gram negative:
Acinetobacter spp. +$
Burkholderia cepacia

Citrobacter freundii
Enterobacter spp.
*Escherichia coli**
Klebsiella spp.
Proteus, indole positive
Pseudomonas aeruginosa *
Pseudomonas spp. *
Pseudomonas stutzeri [$]
Serratia spp.
Anaerobes, Gram negative:
Bacteroides spp. *
Inherently resistant organisms
Aerobes, Gram positive:
Corynebacterium jeikeium
Staphylococcus spp. *methicillin resistant*
Aerobes, Gram negative
Legionella spp.
Stenotrophomonas maltophilia [+$]

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

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 metabolized 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 kind 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

The product does not contain any excipient or preservative.

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 aminoglycosid. 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 hydrogen carbonate.

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:
Please see the expiry date on package
Storage condition: Do not store above 30°C

After reconstitution (and dilution):
Chemical and physical after reconstitution has been demonstrated for 24 hours at 30°C and for 48 hours at 2-8°C.
Chemical and physical after reconstitution and dilution has been demonstrated for 24 hours at 30°C and for 1 week 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

This medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

TAZOPET:
Filled in 50 ml clear, colourless glass vial and packed in carton with pack sizes of 1,2,3,5,6,10,12,50 and 100 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.
For single use only. Discard any unused solution.

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

Reconstitution directions (to intravenous injection)
Each vial should be reconstituted with 20 ml diluent.

Sterile diluents for preparation of the reconstituted solution:
- Sterile 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

Swirl until dissolved. Intravenous injection should be given over at least 3-5 minutes.

Dilution directions (to intravenous infusion)
Each vial should be reconstituted with 20 ml of the above diluents.
The reconstituted solution may be further diluted to 50 ml with sterile water for injection and to 50,100 or 150 ml with one of the following sterile diluents:
- Sodium chloride 9 mg/ml (0.9 %) solution in water for injection
- Glucose 50 mg/ml (5 %) solution in water for injection
- Dextran 6% in saline

Intravenous infusion should be given over 20-30 minutes.

7. MANUFACTURER

Shandong Anxin Pharmaceutical Co. Ltd., Jinan, Shandong, China

8. IMPORTER

Sandoz (Thailand) Limited, Bangkok, Thailand

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9. DATE OF REVISION OF THE TEXT

10 September 2024; CDSv06_01_2022