SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT
TAZOPENIL 4 g/0.5 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
TAZOPENIL 4 g/0.5 g powder for solution for infusion
Each glass vial contains 4 g of piperacillin (as the sodium salt) and 0.5 g tazobactam (as the sodium salt).

Excipients with known effects: each vial of Tazopenil 4 g/0.5 g contains 9.40 mmol (216 mg) of sodium.

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

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia.
- Complicated urinary tract infections (including pyelonephritis).
- Complicated intra-abdominal infections.
- Complicated skin and soft tissue infections (including diabetic foot infections).

Treatment of patients with bacteraemia in association, or suspected association, with any of the infections listed above.
Tazopenil may be used in the treatment of neutropenic patients with fever suspected to be caused by bacterial infection.

Children between 2 and 12 years
- Complicated intra-abdominal infections

Tazopenil may be used in the treatment of neutropenic children with fever suspected to be caused by bacterial infection.

The appropriate use of antibacterial agents should be in accordance with official guidelines.
4.2 Posology and method of administration
Posology
The dose and frequency of administration of Tazopenil depend on the severity and site of the infection and the expected pathogens.

Adults and adolescents
Infections
The usual dosage for adults and children aged 12 years and over with normal renal function is from a minimum of 2 g / 0.25 g to a maximum of 4 g / 0.5 g piperacillin and tazobactam administered every 6, 8 or 12 hours.

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

For hospital-acquired pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin/0.5 g tazobactam administered every 6 hours. This posology may also be appropriate for the treatment of patients with other infections included in the therapeutic indications, if they are particularly severe.
The following table summarises the administration frequency and the recommended dose for adults and adolescents, based on indication or pathology:

Treatment frequency	**Tazopenil 4 g / 0,5 g**
Every 6 hours	Severe pneumonia
	Neutropenic patients with fever suspected to be caused by bacterial infection
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Patients with renal failure
The intravenous dose should be adjusted according to the degree of actual renal impairment, as follows (each patient should be carefully monitored for signs of toxicity caused by the substance; the dose and the administration interval of the medicinal product should be adjusted accordingly):

Creatinine clearance (ml/min)	**Tazopenil (recommended dose)**
> 40	No dose adjustment is required
20 - 40	Maximum dose recommended 4 g/0.5 g every 8 hours
< 20	Maximum dose recommended 4 g/0.5 g every 12 hours

For haemodialysis patients, an additional dose of piperacillin/tazobactam 2 g / 0.25 g should be administered after each dialysis session, as 30% - 50% of piperacillin is eliminated by haemodialysis in 4 hours.

Patients with hepatic failure
No dose adjustment is required (See section 5.2).

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

Paediatric population (2-12 years)

Infections
The following table summarises the treatment frequency and the recommended dose per body weight for paediatric patients aged 2 to 12, for adults and adolescents, based on indication or pathology:

Dose per weight and administration frequency	**Indication / pathology**
80 mg piperacillin / 10 mg tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be caused by bacterial infection*
100 mg piperacillin / 12.5 mg tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

*Do not exceed maximum dose of 4 g / 0.5 g per dose over 30 minutes.

Patients with renal failure
The intravenous dose should be adjusted according to the actual degree of renal impairment, as follows (each patient should be carefully monitored for signs of toxicity caused by the substance; the dose and the administration interval of the medicinal product should be adjusted accordingly):

Creatinine clearance (ml/min)	Tazopenil (Recommended dose)
> 50	No dose adjustment is required
≤ 50	70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours.

For haemodialysis paediatric patients, an additional dose of 40 mg piperacillin/5 mg tazobactam/kg should be administered after each dialysis session.

Use in children under 2 years of age
Safety and efficacy of Tazopenil in children aged 0 to 2 years have not been established.
No data available from controlled clinical studies.

Duration of treatment
The usual duration of treatment for most indications is between 5 and 14 days.
However, the duration of treatment should be determined according to the severity of the infection, the pathogen(s) and the clinical and bacteriological evolution of the patient.

Route of administration
TAZOPENIL 4 g/ 0.5 g is administered by slow intravenous injection or by intravenous infusion (a drip for 30 minutes).

For reconstitution of the medicinal product instructions prior to administration, see section 6.6.

4.3 Contraindications
Hypersensitivity to the active ingredients, to any other penicillin antibacterial agent or to any of the excipients listed in section 6.1.
Positive anamnesis for acute severe allergic reaction to any other beta-lactam active substance (e.g. cephalosporin, monobactam or carbapenem).

4.4 Special warnings and precautions for use
Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH have been reported in patients treated with Tazopenil, often after treatment lasting more than 10 days. HLH is a life-threatening pathological immune activation syndrome characterised by clinical signs and symptoms of excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenemia, elevated serum ferritin, cytopenias and haemophagocytosis). Patients showing the first signs of pathological immune activation should be examined immediately. If HLH is diagnosed, treatment with tazopenil should be discontinued.

The choice of piperacillin/tazobactam for the individual treatment of a patient should considered the appropriateness of using a semi-synthetic broad-spectrum penicillin, based on factors such as the severity of the infection and the prevalence of resistance to other available antibacterial agents.

Prior to initiating therapy with Tazopenil, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Severe and occasionally fatal hypersensitivity reactions (anaphylactic/anaphylactoid [including shock]) have been reported in patients receiving penicillin therapy, including piperacillin/tazobactam. Such reactions are more likely to occur in individuals with a positive

anamnesis for sensitivity to multiple allergens. Severe hypersensitivity reactions require discontinuation of the antibiotic and may require administration of epinephrine and other emergency measures.

Tazopenil 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 skin rashes have to be carefully monitored and if the lesions worsen, piperacillin/tazobactam 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, Tazopenil should be discontinued.

Therapy with Tazopenil may result in the emergence of resistant organisms, which might cause super-infections.

Bleeding episodes have occurred in some patients receiving beta-lactam antibiotics.
These reactions sometimes have been associated with abnormal coagulation tests, such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding episodes 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 such as convulsions may occur when high doses are administered, especially in patients with renal impairment.

Each vial of Tazopenil 4 g / 0.5 g contains 216 mg of sodium, equivalent to 10.8% of the maximum daily intake recommended by the WHO, which corresponds to 2 g of sodium for an adult. It must be taken into consideration in people with reduced kidney function or on a low-sodium content 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 caution in patients with renal impairment or on haemodialysis. Intravenous dosages and dosing intervals should be adjusted according to the degree of renal impairment (see section 4.2).
In a secondary analysis using data from a large multicentre randomised controlled trial, when the glomerular filtration rate (GFR) after administration of frequently used antibiotics in critically ill patients was examined, the use of piperacillin/tazobactam was associated with a lower rate of reversible improvement in GFR compared to other antibiotics. As per this secondary analysis, it was concluded that piperacillin/tazobactam was a cause of delayed recovery of renal function in these patients.

4.5 Interaction with other medicinal products and other forms of interaction
Non-depolarising muscle relaxants
Piperacillin, when used concurrently with vecuronium, has been reported to prolong vecuronium-induced neuromuscular blockade. It is expected that neuromuscular blockade produced by any non-depolarising muscle relaxant may be prolonged in the presence of piperacillin, due to its similar mechanism of action

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 methotrexate excretion; therefore, patients' serum methotrexate levels must be monitored to avoid toxicity from the medicinal substance.

Probenecid
As with other penicillins, concomitant administration of probenecid and piperacillin/tazobactam prolongs the half-life and reduces the renal clearance of both piperacillin and tazobactam; however, this does not affect the peak plasma concentrations of both substances.

Aminoglycosides
Piperacillin, either as single-agent therapy or in combination with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and mild to moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam and the M1 metabolite were not significantly altered by tobramycin administration.
Inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

For information regarding the administration of piperacillin/tazobactam in combination with aminoglycosides, see sections 6.2 and 6.6.

Vancomycin
Pharmacokinetic interactions between piperacillin/tazobactam and vancomycin have not been observed.
However, a limited number of retrospective studies have identified an increased incidence of acute kidney injury in patients receiving concurrently piperacillin/tazobactam and vancomycin compared to vancomycin alone.

Effect on laboratory tests
As with other penicillins, the use of non-enzymatic methods to measure glycosuria may lead to false positive results. Therefore, measurement of glycosuria by enzymatic methods is required for therapy with Tazopenil.

Several chemical methods for measuring proteinuria can lead to false positive results. Protein measurement with dip sticks is not affected.

The direct Coombs test may be positive.

Platelia Aspergillus EIA tests conducted by Bio-Rad Laboratories in patients treated with Tazopenil may lead to false positive results. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses have been reported with the Bio-Rad Laboratories *Platelia Aspergillus* EIA test.

In patients treated with Tazopenil, positive results obtained by the methods listed above should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and breast-feeding
Pregnancy
Data on the use of Tazopenil in pregnant women are either non-existent or very scarce.

Animal studies have shown toxicity during animal development, but there is no evidence of teratogenic effects when the medicinal product has been used at doses toxic to the mother (see section 5.3).

Piperacillin and tazobactam cross the placental barrier. Piperacillin/tazobactam should be used during pregnancy only if clearly indicated, that is, if the expected benefit outweighs the possible risks to the pregnant woman and to the foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in breast milk; concentrations of tazobactam in breast milk have not been studied. Breast-feeding women 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
Studies on the ability to drive and use machines have not been performed.

4.8 Undesirable effects
The most commonly reported adverse reaction is diarrhoea (occurring in 1 in 10 patients). Among the most serious adverse reactions, pseudomembranous colitis and toxic epidermal necrolysis occur in 1-10 patients per 10,000. The frequencies of pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be defined on the basis of currently available data.

In the following table, adverse reactions are listed by to system-organ classification and MedDRA nomenclature. Within each frequency group, undesirable effects are listed in descending order of severity.

Systemic-organic classification	**Very common** *≥ 1/10*	**Common** *≥1/100,<1/10*	**Uncommon** *≥1/1,000,<1/100*	**Rare** *≥1/10,000,<1/1,000*	**Not known frequency** ***not definable on the basis of available data***
Infections and infestations		Candida infection*		pseudomembranous colitis	
Blood and lymphatic system disorders		Thrombocytopenia, anaemia*	Leukopenia,	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*, eosinophilia*
Immune system disorders					anaphylactoid shock*, anaphylactoid shock*, anaphylactic reaction*, hypersensitivity*
Metabolism and nutrition disorders			Hypokalaemia		,
Psychiatric disorders		insomnia			
Nervous system disorders		headache			
Vascular disorders			Hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory thoracic and mediastinal disorders				epistaxis	Eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, constipation, nausea, dyspepsia		stomatitis	
Hepatobiliary disorders					Hepatitis*, jaundice
Skin and		Rash, itch	Erythema	toxic epidermal	Stevens-Johnson

subcutaneous tissue disorders			multiforme*, urticaria, maculo-papular rash*	necrolysis*	syndrome*, exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, bullous dermatitis, purpura
Musculoskeletal system and connective tissue disorders			Arthralgia, myalgia		
Renal and urinary disorders					Renal insufficiency, tubulointerstitial nephritis*
General disorders and administration site conditions		Pyrexia, injection site reaction	Chills		
Diagnostic tests		increased alanine aminotransferase, increased aspartate aminotransferase, decreased total protein, decreased blood albumin, positive direct Coombs test, increased blood creatinine, increased blood alkaline phosphatase, increased blood urea levels, prolonged activated partial thromboplastin time	Reduction in blood glucose, increase in blood bilirubin, prolongation of prothrombin time		Prolongation of bleeding time, increase in gamma-glutamyl-transferase

**Post-marketing identified ADRs*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction via the Italian national reporting system to this address www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose

Symptoms

Post-marketing reports of overdose with piperacillin/tazobactam have been reported. Most of the reported events, including nausea, vomiting and diarrhoea, have been reported even with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended intravenous doses are administered (particularly in the presence of renal impairment).

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

Treatment should be supportive and symptomatic according to the patient's clinical picture.
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, Combination of penicillins including beta-lactamase inhibitors; ATC code: J01CR05.

Mechanism of action
Piperacillin, is a broad spectrum and semi-synthetic penicillin that 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 Amp enzymes or metallo-beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

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.

Breakpoint

EUCAST Clinical MIC Breakpoints for Piperacillin / Tazobactam (02-12-2009, v 1). For Sensitivity 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 sensitivity of *streptococci* is inferred from the penicillin sensitivity.
The sensitivity of *staphylococci* is inferred from the oxacillin sensitivity.

Sensitivity

The prevalence of acquired resistance may vary geographically and over time for certain species, so it is desirable to acquire local information on resistance, particularly when treating serious infections. Expert advice should be sought when the local prevalence of resistance is such that the usefulness of the substance is questionable, at least in certain types of infections.

Classification of relevant species into groups according to sensitivity to piperacillin/tazobactam
COMMONLY SENSITIVE SPECIES
Gram-positive Aerobic Bacteria *Enterococcus faecalis* *Listeria monocytogenes* *Staphylococcus aureus,* methicillin-sensitive[£] *Staphylococcus species, coagulasi-negativo*, methicillin-sensitive *Streptococcus pyogens* *Group B streptococcus*
Gram-negative Aerobic Bacteria *Citrobacter koseri* *Haemophilus influenza* *Moraxella catarrhalis* *Proteus mirabilis*
Gram-positive Anaerobic Bacteria *Clostridium species* *Eubacterium species* *Peptostreptococcus species*
Gram-negative Anaerobic Bacteria *Bacteroides fragilis Group* *Eubacterium species* *Porphyromonas species* *Prevotella species*
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Gram-positive Aerobic Bacteria *Enterococcus faecium*[$,+] *Streptococcus pneumonia* *Streptococcus viridans group* Gram-negative Aerobic Bacteria *Acinetobacter baumannii*[$] *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter species* *Escherichia coli* *Klebsiella penumonia* *Morganella morganii* *Proteus vulgaris* *Providencia ssp.* *Pseudomonas aeruginosa* *Serratia species*
INHERENTLY RESISTANT ORGANISMS
Gram-positive Aerobic Bacteria *Corynebacterium jeikeium* Gram-negative Aerobic Bacteria *Legionella species* *Stenotrophomonas maltophilia*[+,$]
Other microorganisms
Chlamydophilia pneumonia *Mycoplasma pneumonia*
[$]Species showing natural intermediate sensitivity. [+]Species for which high-resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU. [£]All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

5.2 Pharmacokinetic properties

Absorption

Piperacillin and tazobactam is rapidly absorbed after intramuscular administration, with a bioavailability of 71% for the piperacillin and 84% for the tazobactam. The plasma concentration peak of TAZOPENIL is detected immediately after the end of the intravenous infusion and after 40-50 minutes after the intramuscular administration.

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 are 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 microbiologically active minor metabolite (desethyl-metabolite). Tazobactam is metabolised to a single, microbiologically inactive metabolite.

Elimination

Piperacillin and tazobactam are eliminated by 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 remaining 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 pharmacokinetics 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 of 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent from 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
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 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 foetuses 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 foetal 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 rats.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Not present.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever TAZOPENIL is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately.

The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

TAZOPENIL should not be mixed with other substances in a syringe or bottle since compatibility has not been established.

Because of chemical instability, TAZOPENIL should not be used with solutions containing only sodium carbonate.

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

6.3 Shelf life
Sealed vial: 3 years

Reconstituted solution in a vial

After reconstitution the solution should be administered immediately.
Unused solution must be discarded

6.4 Special precautions for storage
Sealed vial: Do not store at temperatures over 25°C.
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container
10 type II glass powder vial with a bromo-butyl rubber cap and flip-off seal, containing 4 g of piperacillin and 0.5 g of tazobactam.

Maybe not all packages are marketed.

6.6 Special precautions for disposal and other handling
Reconstitution and dilution should be carried out under aseptic conditions. The solution should be examined visually before administration to discard any particulate matter and discolouration. The solution should only be used if it is clear and free from particulate matter.

Intravenous use
Reconstitute one vial with the volume of solvent given in the table below, using one of the compatible solvents for reconstitution. Shake with a circular movement until dissolved. With constant rotation, reconstitution generally takes 5 to 10 minutes (see below for more information on handling).

Vial content	Volume of solvent* to be added to the vial
4 g/0.5 g (4 g piperacillin and 0.5 g tazobactam)	*20 ml*

**Compatible solvents for reconstitution:*
- Sterile water for injectable preparations
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%

Shake the vial containing the lyophilisate to be reconstituted to detach the powder from its bottom.
Using a syringe, take a suitable solvent and drop it in the vial containing the lyophilisate.
Shake vigorously until the powder is completely dissolved. Reconstitution should occur within 10 minutes with constant shaking.
Let the solution to stand until the foam has disappeared and a clear solution is obtained. Make sure that there are no undissolved residual particles before taking with a suitable syringe.
The reconstituted solution should be taken from the vial with a syringe. Once reconstituted according to the instructions, the contents of the vial taken with the syringe will provide the amount of piperacillin and tazobactam indicated on the label.
Reconstituted solutions may be further diluted to the desired volume (e.g. 50 to 150 ml) with one of the following compatible solvents:
- Sterile water for injectable preparations (*the maximum recommended volume of sterile water for preparations for injection per dose is 50 ml)*
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Dextran 6% in 0.9% (9 mg/ml) sodium chloride

Co-administration with aminoglycosides
Due to the *in vitro* inactivation of aminoglycoside by beta-lactam antibiotics, it is recommended that Tazopenil and aminoglycoside be administered separately. When concomitant therapy with aminoglycosides is indicated, Tazopenil and the aminoglycoside should be reconstituted and diluted separately.

For incompatibilities, see section 6.2.

Medicines no longer used or medical waste should be disposed of in compliance with the local regulations in force.
For single use only. Any unused product should be disposed of.

7. MARKETING AUTHORISATION HOLDER
Magis Farmaceutici S.r.l. - Via Cefalonia, 70 - 25124 - Brescia

8. MARKETING AUTHORISATION NUMBER(S)
TAZOPENIL 4 g/0.5 g powder for solution for infusion - 10 small bottle of powder
AIC No. 038181032

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
July 2018

10. DATE OF REVISION OF THE TEXT
January 2022