Annex III

Summary of product characteristics, labelling and package leaflet

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tazocin and associated names (see Annex I) 2 g / 0.25 g powder for solution for infusion

Tazocin and associated names (see Annex I) 4 g / 0.5 g powder for solution for infusion

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.

Each vial of Tazocin 2 g / 0.25 g contains 5.58 mmol (128 mg) of sodium.

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

Each vial of Tazocin 4 g / 0.5 g contains 11.16 mmol (256 mg) of sodium.

Excipients:

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

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

Adults and adolescents

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

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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

Children 2 to 12 years of age

- Complicated intra-abdominal infections

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

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

4.2 Posology and method of administration

Posology

The dose and frequency of Tazocin 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	**Tazocin 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)	**Tazocin (recommended dose)**
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours.

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)	Tazocin (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 Tazocin 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
Tazocin 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).

Tazocin 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 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 Tazocin, 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.

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 Tazocin, should be discontinued.

Therapy with Tazocin 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 Tazocin 2 g / 0.25 g contains 5.58 mmol (128 mg) of sodium and Tazocin 4 g / 0.5 g contains 11.16 mmol (256 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.

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

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 Tazocin 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 Tazocin. 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 Tazocin 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 Tazocin 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 reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**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)
Infections and infestations		candidal superinfection		
Blood and lymphatic system disorders		leukopenia, neutropenia, thrombocytopenia	anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia	agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia

Immune system disorders		hypersensitivity	anaphylactic/ anaphylactoid reaction (including shock)	
Metabolism and nutrition disorders				hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, thrombophlebitis, phlebitis	flushing	
Gastrointestinal disorders	diarrhoea, vomiting, nausea	jaundice, stomatitis, constipation, dyspepsia	pseudo-membranous colitis, abdominal pain	
Hepatobiliary disorders		alanine aminotransferase increased, aspartate aminotransferase increased	hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltrans-ferase increased	
Skin and subcutaneous tissue disorders	rash, including maculopapular rash	urticaria, pruritus	erythema multiforme, dermatitis bullous, exanthema	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	
Renal and urinary disorders		blood creatinine increased	renal failure, tubulointerstitial nephritis	blood urea increased
General disorders and administration site conditions		pyrexia, injection-site reaction	chills	

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

Treatment

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05

Mechanism of action

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporinsbut it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / Pharmacodynamic relationship

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

Mechanism of resistance

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

- Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.

- Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.

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

Breakpoints

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

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to piperacillin / tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Listeria monocytogenes* *Staphylococcus aureus*, methicillin-susceptible[£] *Staphylococcus* species, *coagulase negative*, methicillin-susceptible *Streptococcus pyogenes* *Group B streptococci*
Aerobic Gram-negative micro-organisms *Citrobacter koseri* *Haemophilus influenza* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobic Gram-positive micro-organisms *Clostridium* species *Eubacterium* species *Peptostreptococcus* species
Anaerobic Gram-negative micro-organisms *Bacteroides fragilis* group *Fusobacterium* species *Porphyromonas* species *Prevotella* species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecium[$,+]
Streptococcus pneumonia
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii[$]
Burkholderia cepacia
Citrobacter freundii
Enterobacter species
Escherichia coli
Klebsiella pneumonia
Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Corynebacterium jeikeium
Aerobic Gram-negative micro-organisms
Legionella species
Stenotrophomonas maltophilia[+,$]
Other microorganisms
Chlamydophilia pneumonia
Mycoplasma pneumonia
[$] 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. [£] All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

5.2 Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.

Distribution

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

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

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

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

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

Special populations

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 ml/min compared to patients with normal renal function.

Haemodialysis removes 30% to 50% of piperacillin / tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.

Paediatric population
In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) ml/min/kg. The piperacillin clearance estimate is 80% of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

Elderly patients
The mean half-life for piperacillin and tazobactam were 32% and 55% longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

Race
No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

5.3 Preclinical safety data

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 fetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.
Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin / tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam in the rat.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate disodium (EDTA)
Citric acid monohydrate

6.2 Incompatibilities

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

Whenever Tazocin 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.

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

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

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

6.3 Shelf life

Unopened vial: 3 years

Reconstituted solution in vial

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 25°C and for 48 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution

After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours at 25°C and for 48 hours when stored in a refrigerator at 2-8°C, when

reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions 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 12 hours at 2-8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: Do not store above 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

30 ml Type I glass vial with a bromo-butyl rubber stopper and flip-off seal.

70 ml Type I glass vial with a bromo-butyl rubber stopper and flip-off seal.

Pack sizes: 1, 5, 10, 12 or 25 vials per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Intravenous use

Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes (for details on handling, please see below).

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

* Compatible solvents for reconstitution:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections(1)
- Glucose 5%

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

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

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%

- Dextran 6% in 0.9% sodium chloride
- Lactated Ringers injection
- Hartmann's solution
- Ringer's acetate
- Ringer's acetate/malate

Co-administration with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Tazocin and the aminoglycoside are recommended for separate administration. Tazocin and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

In circumstances where co-administration is recommended, Tazocin is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Tazocin Dose	Tazocin diluent volume (ml)	Aminoglycoside concentration range* (mg/ml)	Acceptable diluents
Amikacin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

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

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

See section 6.2 for incompatibilities.

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

For single use only. Discard any unused solution.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this product is available on the website of:

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND VIALS

1. NAME OF THE MEDICINAL PRODUCT

Tazocin and associated names (see Annex I) 2 g / 0.25 g powder for solution for infusion

Tazocin and associated names (see Annex I) 4 g / 0.5 g powder for solution for infusion

Piperacillin / tazobactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 2 g piperacillin (as sodium salt) and 0.25 g tazobactam (as sodium salt).
Each vial contains: 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt).

3. LIST OF EXCIPIENTS

Edetate disodium (EDTA) and citric acid monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for infusion.
5 x 1 vial with powder for solution for infusion.
10 x 1 vial with powder for solution for infusion.
12 x 1 vial with powder for solution for infusion.
25 x 1 vial with powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials: Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tazocin
2 g / 0.25 g powder for solution for infusion
Tazocin
4 g / 0.5 g powder for solution for infusion
piperacillin / tazobactam

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TAZOCIN IS AND WHAT IT IS USED FOR

Piperacillin belongs to the group of medicines known as “broad-spectrum penicillin antibiotics”. It can kill many kinds of bacteria. Tazobactam can prevent some resistant bacteria from surviving the effects of piperacillin. This means that when piperacillin and tazobactam are given together, more types of bacteria are killed.

TAZOCIN is used in adults and adolescents to treat bacterial infections, such as those affecting the lower respiratory tract (lungs), urinary tract (kidneys and bladder), abdomen, skin or blood. TAZOCIN may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

TAZOCIN is used in children aged 2-12 years to treat infections of the abdomen such as appendicitis, peritonitis (infection of the fluid and lining of the abdominal organs), and gallbladder (biliary) infections. TAZOCIN may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

In certain serious infections, your doctor may consider using TAZOCIN in combination with other antibiotics.

2. BEFORE YOU USE TAZOCIN

Do not use TAZOCIN
- if you are allergic (hypersensitive) to piperacillin or tazobactam or any of the other ingredients of TAZOCIN.
- if you are allergic (hypersensitive) to antibiotics known as penicillins, cephalosporins or other beta-lactamase inhibitors, as you may be allergic to TAZOCIN.

Take special care with TAZOCIN
- if you have allergies. If you have several allergies, make sure you tell your doctor or other healthcare professional before receiving this product.
- if you are suffering from diarrhoea before, or if you develop diarrhoea during or after your treatment. In this case, make sure you tell your doctor or other healthcare professional immediately. Do not take any medicine for the diarrhoea without first checking with your doctor.
- if you have low levels of potassium in your blood. Your doctor may want to check your kidneys before you take this medicine and may perform regular blood tests during treatment.
- if you have kidney or liver problems, or are receiving haemodialysis. Your doctor may want to check your kidneys before you take this medicine, and may perform regular blood tests during treatment.
- if you are taking certain medicines (called anticoagulants) to avoid an excess of blood clotting (see also **Using other medicines** in this leaflet) or any unexpected bleeding occurs during the treatment. In this case, you should inform your doctor or other healthcare professional immediately.
- if you develop convulsions during the treatment. In this case, you should inform your doctor or other healthcare professional.
- if you think you developed a new or worsening infection. In this case, you should inform your doctor or other healthcare professional.

Children below 2 years

Piperacillin / tazobactam is not recommended for use in children below the age of 2 years due to insufficient data on safety and effectiveness.

Using other medicines
Please tell your doctor or other healthcare professional if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may interact with piperacillin and tazobactam.
These include:
- medicine for gout (probenecid). This can increase the time it takes for piperacillin and tazobactam to leave your body.
- medicines to thin your blood or to treat blood clots (e.g. heparin, warfarin or aspirin).
- medicines used to relax your muscles during surgery. Tell your doctor if you are going to have a general anaesthetic.
- methotrexate (medicine used to treat cancer, arthritis or psoriasis). Piperacillin and tazobactam can increase the time it takes for methotrexate to leave your body.
- medicines that reduce the level of potassium in your blood (e.g. tablets enhancing urination or some medicines for cancer).
- medicines containing the other antibiotics tobramycin or gentamycin. Tell your doctor if you have kidney problems.

Effect on laboratory tests
Tell the doctor or laboratory staff that you are taking TAZOCIN if you have to provide a blood or urine sample.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are trying to become pregnant, tell your doctor or other healthcare professional before receiving this product. Your doctor will decide if TAZOCIN is right for you.

Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are breast-feeding, your doctor will decide if TAZOCIN is right for you.

Driving and using machines
The use of TAZOCIN is not expected to affect the ability to drive or use machines.

*Important information about some of the ingredients of **TAZOCIN***
TAZOCIN 2 g / 0.25 g contains 5.58 mmol (128 mg) of sodium.

TAZOCIN 4 g / 0.5 g contains 11.16 mmol (256 mg) of sodium.

This should be taken into consideration if you are on a controlled-sodium diet.

3. HOW TO USE TAZOCIN

Your doctor or other healthcare professional will give you this medicine through an infusion (a drip for 30 minutes) into one of your veins. The dose of medicine given to you depends on what you are being treated for, your age, and whether or not you have kidney problems.

Adults and adolescents aged 12 years or older

The usual dose is 4 g / 0.5 g of piperacillin / tazobactam given every 6-8 hours, which is given into one of your veins (directly into the blood stream).

Children aged 2 to 12 years

The usual dose for children with abdominal infections is 100 mg / 12.5 mg / kg of body weight of piperacillin / tazobactam given every 8 hours into one of your veins (directly into the blood stream). The usual dose for children with low white blood cell counts is 80 mg / 10 mg / kg of body weight of piperacillin / tazobactam given every 6 hours into one of your veins (directly into the blood stream).

Your doctor will calculate the dose depending on your child's weight but the daily dose will not exceed 4 g / 0.5 g of TAZOCIN.

You will be given TAZOCIN until the sign of infection has gone completely (5 to 14 days).

Patients with kidney problems

Your doctor may need to reduce the dose of TAZOCIN or how often you are given it. Your doctor may also want to test your blood to make sure that your treatment is at the right dose, especially if you have to take this medicine for a long time.

*If you receive more **TAZOCIN** than you should*
As you will receive TAZOCIN from a doctor or other healthcare professional, you are unlikely to be given the wrong dose. However, if you experience side effects, such as convulsions, or think you have been given too much, tell your doctor immediately.

*If you miss a dose of **TAZOCIN***
If you think you have not been given a dose of TAZOCIN, tell your doctor or other healthcare professional immediately.

If you have any further questions on the use of this product, ask your doctor or other healthcare professional.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TAZOCIN can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or other healthcare professional.

The serious side effects of Tazocin are:
-swelling of the face, lips, tongue or other parts of the body
-shortness of breath, wheezing or trouble breathing
-severe rash, itching or hives on the skin
-yellowing of the eyes or skin
-damage to blood cells (the signs include: being breathless when you do not expect it, red or brown urine, nosebleeds and bruising)

If you notice any of the above, see a doctor straight away. For frequency of these reactions, refer to the information below.

Possible side effects are listed according to the following categories:
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000

Common side effects:
- diarrhoea, vomiting, nausea
- skin rashes

Uncommon side effects:
- thrush
- (abnormal) decrease in white blood cells (leukopenia, neutropenia) and platelets (thrombocytopenia)
- allergic reaction
- headache, sleeplessness
- low blood pressure, inflammation of the veins (felt as tenderness or redness in the affected area)
- jaundice (yellow staining of the skin or whites of the eyes), inflammation of the mucous lining of the mouth, constipation, indigestion, stomach upset
- increase of certain enzymes in the blood (alanine aminotransferase increased, aspartate aminotransferase increased)
- itching, nettle rash
- increase of muscle metabolism product in the blood (blood creatinine increased)
- fever, injection site reaction
- yeast infection (candidal superinfection)

Rare side effects:
- (abnormal) decrease of red blood cells or blood pigment / haemoglobin, (abnormal) decrease of red blood cells due to premature breakdown (degradation) (haemolytic anaemia), small spot bruising (purpura), bleeding of the nose (epistaxis) and bleeding time prolonged, (abnormal) increase of a specific type of white blood cells (eosinophilia)
- severe allergic reaction (anaphylactic/anaphylactoid reaction, including shock)
- flushed red skin
- a certain form of infection of the colon (pseudomembranous colitis), abdominal pain
- inflammation of the liver (hepatitis), increase of a blood pigments breakdown product (bilirubin), increase of certain enzymes in the blood (blood alkaline phosphatase increased, gamma-glutamyltransferase increased)

- skin reactions with redness and formation of skin lesions (exanthema, erythema multiforme), skin reactions with blistering (bullous dermatitis)
- joint and muscle pain
- poor kidney functions and kidney problems
- rigors chill / rigidity

Very rare side effects:
- severe decrease of granular white blood cells (agranulocytosis), severe decrease of red blood cells, white blood cells and platelets (pancytopenia)
- prolonged time for blood clot formation (prolonged partial thromboplastin time, prothrombin time prolonged), abnormal lab test (positive direct Coombs), increase of platelets (thrombocythaemia)
- decrease of potassium in the blood (hypokalaemia), decrease of blood sugar (glucose), decrease of the blood protein albumin, decrease of blood total protein
- detachment of the top layer of the skin all over the body (toxic epidermal necrolysis), serious bodywide allergic reaction with skin and mucous lining rashes and various skin eruptions (Stevens-Johnson Syndrome)
- blood urea nitrogen increased

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

5. HOW TO STORE TAZOCIN

Keep out of the reach and sight of children.

Do not use TAZOCIN after the expiry date which is stated on the carton and vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials: Do not store above 25°C.

For single use only. Discard any unused solution.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What TAZOCIN contains

- The active substances are piperacillin and tazobactam.
  Each vial contains 2 g piperacillin (as sodium salt) and 0.25 g tazobactam (as sodium salt).
  Each vial contains 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt).
- The other ingredients are citric acid monohydrate and edetate disodium (EDTA).

What TAZOCIN looks like and contents of the pack

TAZOCIN 2 g / 0.25 g is a white to off-white powder supplied in a vial.
Packs containing 1, 5, 10, 12 or 25 vials.

TAZOCIN 4 g / 0.5 g is a white to off-white powder supplied in a vial.
Packs containing 1, 5, 10, 12 or 25 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[See Annex I - To be completed nationally]

Manufacturer:
[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

Detailed information on this medicine is available on the website:

The following information is intended for medical or healthcare professionals only:

Instructions for use
TAZOCIN will be given by intravenous infusion (a drip for 30 minutes).

Intravenous use
Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes (for details on handling, please see below).

Content of vial	**Volume of solvent* to be added to vial**
2 g / 0.25 g (2 g piperacillin and 0.25 g tacobactam)	10 ml
4 g / 0.50 g (4 g piperacillin and 0.5 g tacobactam)	20 ml

*Compatible solvents for reconstitution:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections(1)
- Glucose 5%

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

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

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Dextran 6% in 0.9% sodium chloride
- Lactated Ringers injection
- Hartmann's solution

- Ringer's acetate
- Ringer's acetate/malate

Incompatibilities
Whenever TAZOCIN is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with aminoglycosides, *in vitro,* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible with TAZOCIN *in vitro* in certain diluents at specific concentrations (see **Co-administration of TAZOCIN with aminoglycosides** below).

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

Because of chemical instability, TAZOCIN should not be used with solutions containing only sodium bicarbonate.

TAZOCIN is compatible with lactated Ringer's solution and for co-administration via a Y-site.

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

Co-administration of TAZOCIN with aminoglycosides
Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, TAZOCIN and the aminoglycoside are recommended for separate administration. TAZOCIN and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

In circumstances where co-administration is recomended, TAZOCIN is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	**TAZOCIN Dose**	**TAZOCIN Diluent volume (ml)**	**Aminoglycoside concentration range* (mg/ml)**	**Acceptable diluents**
Amikacin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

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

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