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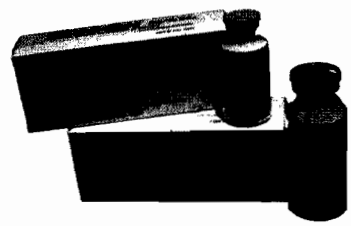

23rd April 2009
(ref: D0C/188/220409o)

RE: Tazocin® 2g/0.25g Powder for Solution for Injection or Infusion
Tazocin® 4g/0.5g Powder for Solution for Injection or Infusion

Dear Health Care Professional,

We would like to bring to your attention information relating to 'new formulation' Tazocin and to emphasise that this information is applicable to reformulated Tazocin® (piperacillin/tazobactam) only. The reformulated Tazocin® incorporates two additional excipients, edetate disodium dihydrate (EDTA) and citric acid.

The addition of these excipients to Tazocin® has enhanced its physical compatibility. The reformulated Tazocin® is now compatible with both Hartmann's Solution and Lactated Ringer's solution and in certain cases with aminogylcosides. It should be noted that 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 reformulated Tazocin® *in vitro* in certain diluents at specific concentrations when administered via a Y tube connection (for details refer to the attached SPC).

Only reformulated Tazocin® is available in the market place and is clearly identifiable by the words "new formulation" on the packaging and vials.

Please note that although the 'new formulation' is available on the market this information will not appear in the technical leaflet in the pack for a number of weeks.

If you wish to report a suspected adverse reaction or medication error contact Wyeth at 01 4493500 or do so via the IMB website www.imb.ie

If you have any questions please contact the Wyeth Medical Information department on 014493500.
Yours sincerely

Dr Declan O'Callaghan
Medical Director

TAZOCIN* 2g/0.25g Powder for Solution for Injection or Infusion
TAZOCIN* 4g/0.5g Powder for Solution for Injection or Infusion

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

TAZOCIN 2g/0.25g Powder for Solution for Injection or Infusion
TAZOCIN 4g/0.5g Powder for Solution for Injection or Infusion

2. Qualitative and Quantitative Composition

TAZOCIN 2g/0.25g Powder for Solution for Injection or Infusion

Each vial contains 2g piperacillin and 0.25g tazobactam (both present as sodium salts).

Each vial of piperacillin/tazobactam contains a total of 128mg of sodium.

TAZOCIN 4g/0.5g Powder for Solution for Injection or Infusion

Each vial contains 4g piperacillin and 0.5g tazobactam (both present as sodium salts).

Each vial of piperacillin/tazobactam contains a total of 256mg of sodium.

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Powder for solution for injection or infusion.
A white to off-white lyophilised powder.

4. Clinical Particulars

4.1. Therapeutic Indications

TAZOCIN is indicated for treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Adults and the Elderly
Lower respiratory tract infections

Urinary tract infections (complicated and uncomplicated)
Intra-abdominal infections
Skin and skin structure infections
Bacterial septicaemia
Bacterial infections in neutropenic adults in combination with an aminoglycoside

Children
Appendicitis complicated by rupture with peritonitis and/or abscess formation in children aged 2-12 years.
Bacterial infections in neutropenic children in combination with an aminoglycoside.

TAZOCIN is indicated for the treatment of polymicrobic infections including those where gram-positive and gram-negative aerobic and/or anaerobic organisms are suspected (intra-abdominal, skin and skin structure, lower respiratory tract) see Section 5.1. As such, TAZOCIN is particularly useful in the treatment of polymicrobial infections and in presumptive therapy prior to the availability of the results of sensitivity tests because of its broad spectrum of activity.

4.2. Posology and Method of Administration

TAZOCIN may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes). For details on reconstitution see section 6.6.

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 TAZOCIN 4g/0.5g (4g piperacillin / 0.5g tazobactam) given every 8 hours.

The total daily dose of TAZOCIN depends on the severity and localisation of the infection and can vary from 2g/0.25g (2g piperacillin / 0.25g tazobactam) to 4g/0.5g (4g piperacillin / 0.5g tazobactam) administered every 6 or 8 hours.

In neutropenia the recommended dose is TAZOCIN 4g/0.5g (4g piperacillin / 0.5g tazobactam) given every 6 hours concomitant with an aminoglycoside.

Elderly with Normal Renal Function

TAZOCIN 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 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 Tazocin (piperacillin/tazobactam) Dosage
20 - 80	13.5g of Tazocin/day (12g piperacillin/1.5g tazobactam) in divided doses of 4.5g (4g piperacillin/ 0.5g tazobactam) q 8H
< 20	9g of Tazocin/day (8g piperacillin/1g tazobactam) in divided doses of 4.5g (4g piperacillin/ 0.5g tazobactam) q 12H

For patients on haemodialysis, the maximum daily dose is 9g of Tazocin (8g piperacillin/1g tazobactam). In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2.25g Tazocin (2g piperacillin/ 0.25g tazobactam) should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAZOCIN will provide additional guidance for adjusting dosage.

Children Aged 12 Years and Under with Normal Renal Function

TAZOCIN is only recommended for the treatment of children with neutropenia or complicated appendicitis.

Neutropenia
For children the dose should be adjusted to 90mg/kg of Tazocin (80mg piperacillin / 10mg tazobactam) administered every 6 hours, concomitant with an aminoglycoside, not exceeding 4.5g of Tazocin (4g piperacillin / 0.5g tazobactam) every 6 hours.

Complicated Appendicitis.
For children aged 2 - 12 years the dose should be adjusted to 112.5mg/kg of Tazocin (100mg piperacillin / 12.5mg tazobactam) administered every 8 hours, not exceeding 4.5g of Tazocin (4g piperacillin / 0.5g tazobactam) every 8 hours.

Until further experience is available, TAZOCIN should not be used in children who do not have neutropenia or complicated appendicitis.

Renal Insufficiency in Children Aged 12 Years and Under

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 Tazocin (piperacillin / tazobactam) Dosage
≥ 40	No adjustment
20-39	90mg Tazocin (80mg piperacillin / 10mg tazobactam) /kg body weight q 8H, not exceeding 13.5g of Tazocin(12g piperacillin/1.5g tazobactam)/day
< 20	90mg Tazocin (80mg piperacillin / 10mg tazobactam) /kg body weight q 12H, not exceeding 9g of Tazocin (8g piperacillin/1g tazobactam)/day

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

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 TAZOCIN should be continued for 48 hours beyond the resolution of clinical symptoms or the fever.

In paediatric complicated appendicitis treatment is recommended for a minimum of 5 days and a maximum of 14 days.

Co-administration of Tazocin

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

In circumstances where co-administration is thought essential, Tazocin containing EDTA in vials has been shown to be compatible for simultaneous co-administration via **Y-site infusion only** with the aminoglycosides; amikacin and gentamicin under certain conditions.

Please see section 6.6 for instructions on dilution and administration.

4.3. Contra-Indications

Hypersensitivity to any of the beta-lactams (including penicillins and cephalosporins) or to beta-lactamase inhibitors.

4.4. Special Warnings and Precautions for Use

Warnings

Serious and occasionally fatal hypersensitivity (anaphylactic / anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins including TAZOCIN. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe reactions when treated with a cephalosporin.

If an allergic reaction occurs during therapy with TAZOCIN, the antibiotic should be discontinued. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Before initiating therapy with TAZOCIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced, life threatening pseudomembranous colitis must be taken into consideration. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Therefore, Tazocin must be discontinued immediately in such cases, and suitable therapy be initiated (e.g. oral metronidazole or oral vancomycin). Preparations which inhibit peristalsis are contra-indicated.

Precautions

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of haematopoietic function should be performed.

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

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

As with other antibiotics, the possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfection. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously, especially in patients with impaired renal function.

This product contains 2.79 mEq (64 mg) of sodium per gram of piperacillin, which may increase a patient's overall sodium intake. This may be harmful to people on a low sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations should be performed in such patients. Modest elevation of indices of liver function may be observed.

Antimicrobials used in high doses for short periods to treat gonorrhoea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhoea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspect primary lesion, and serologic tests should be made for a minimum of 4 months.

4.5. Interactions with other medicinal products and other forms of Interactions

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

Piperacillin either alone or with tazobactam did not cause clinically important alterations to 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 not significantly altered by tobramycin administration. No clinically important pharmacokinetic interactions have been noted between TAZOCIN and vancomycin in healthy adults with normal renal function.

Hartmann's solution or Lactated Ringer's Solution is compatible with Tazocin containing EDTA (see section 6.6)

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

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-polarizing muscle relaxants could be prolonged in the presence of piperacillin.

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

As with other penicillins, the administration of TAZOCIN may result in a false-positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving piperacillin/tazobactam injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

4.6. Pregnancy and Lactation

Studies in mice and rats have not demonstrated any embryotoxic or teratogenic effects of the piperacillin-tazobactam combination Tazocin. There are no adequate and well-controlled studies with piperacillin-tazobactam combination Tazocin or with piperacillin or tazobactam alone in pregnant women. Piperacillin and tazobactam cross the placenta. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

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 nursing woman and child.

4.7. Effects on Ability to Drive and Use Machines

TAZOCIN is not known to affect ability to drive or operate machines.

4.8. Undesirable Effects

The most commonly reported adverse reactions are diarrhoea, nausea, vomiting, and rash, each having a frequency of ≥ 1% but ≤ 10%.

Body System	Adverse Reaction
Infections and infestations:	
Uncommon:	Candidal superinfection
Blood and lymphatic system disorders:	
Uncommon:	Leucopenia, neutropenia, thrombocytopenia
Rare:	Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia
Very rare:	Agranulocytosis, Coombs direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis
Immune system disorders:	
Uncommon:	Hypersensitivity reaction
Rare:	Anaphylactic/anaphylactoid reaction (including shock)
Metabolism and nutritional disorders:	
Very rare:	Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia
Nervous system disorders:	
Uncommon:	Headache, insomnia
Rare:	Muscular weakness, hallucination, convulsion, dry mouth
Vascular disorders:	
Uncommon:	Hypotension, phlebitis, thrombophlebitis
Rare:	Flushing
Gastrointestinal disorders:	
Common:	Diarrhoea, nausea, vomiting
Uncommon:	Constipation, dyspepsia, jaundice, stomatitis
Rare:	Abdominal pain, pseudomembranous colitis, hepatitis

Hepatobiliary disorders:	
Uncommon:	Alanine aminotransferase increased, aspartate aminotransferase increased
Rare:	Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis
Skin and subcutaneous tissue disorders:	
Common:	Rash
Uncommon:	Pruritus, urticaria, erythema
Rare:	Bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema
Very rare:	Stevens-Johnson Syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders:	
Rare:	Arthralgia, myalgia
Renal and urinary disorders:	
Uncommon:	Blood creatinine increased
Rare:	Interstitial nephritis, renal failure
Very rare:	Blood urea nitrogen increased
General disorders and administration site conditions:	
Uncommon:	Fever, injection site reaction
Rare:	Rigors, tiredness, oedema

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

4.9. Overdose

There have been post-marketing reports of overdose with TAZOCIN. The majority of those events experienced including nausea, vomiting, and diarrhoea have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment of Intoxication

No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

In case of motor excitability or convulsions, anticonvulsive agents (e.g. diazepam or barbiturates) may be indicated.

In case of severe, anaphylactic reactions, the usual counter-measures are to be initiated.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

ATC Code: J01CR05
Pharmacotherapeutic group: Beta-lactam antibacterials, penicillins

Piperacillin, a broad spectrum, semisynthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many β-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 TAZOCIN formulation enhances and extends the antibiotic spectrum of piperacillin to include many β-lactamase producing bacteria normally resistant to it and other β-lactam antibiotics. Thus, TAZOCIN combines the properties of a broad spectrum antibiotic and a β-lactamase inhibitor.

TAZOCIN is highly active against piperacillin-sensitive micro-organisms as well as many β-lactamase producing, piperacillin-resistant micro-organisms. TAZOCIN also acts synergistically with aminoglycosides against certain strains of *Pseudomonas aeruginosa*.

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections. Please refer to local guidelines for antibiotic sensitivity testing as appropriate.

The minimum inhibitory concentration (MIC) breakpoints separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are suggested as follows:

PROPOSED MINIMUM INHIBITORY CONCENTRATION (MIC) BREAKPOINTS

Pathogens	Susceptible	Intermediate	Resistant
Enterobacteriaceae	$\leq$ 16 mg/L	32 - 64 mg/L	$\geq$ 128 mg/L
Pseudomonas	$\leq$ 64 mg/L	-	$\geq$ 128 mg/L
Staphylococcus	$\leq$ 8 mg/L	-	$\geq$ 16 mg/L
Streptococcus	$\leq$ 1 mg/L	-	$\geq$ 2 mg/L
Anaerobes	$\leq$ 32 mg/L	64 mg/L	$\geq$ 128 mg/L

Resistance has been mainly observed for *Staphylococcus epidermidis*, *Burkholderia cepacia*, *Citrobacter freundii*, *Enterobacter cloacae*, *Pseudomonas* and *Serratia* species, *Enterococcus avium*, *Enterococcus faecium*, *Propionibacterium acnes*, *Acinetobacter* species, *Enterobacter aerogenes*, *Stenotrophomonas maltophilia*, *Corynebacterium jeikeium*, *Staphylococcus aureus* (methicillin resistant), and *Staphylococcus* coagulase negative (methicillin resistant).

Organism susceptibility to TAZOCIN observed in the European clinical studies conducted in adults or children with various infections published from 1997 to 1999 have been summarised in the following table.

It must be noted that this information gives only an approximate guidance on the probability that a micro-organism will be susceptible to TAZOCIN.

ESTIMATED EUROPEAN RANGE OF MICROBIOLOGIC RESISTANCE TO TAZOCIN (PIPERACILLIN/TAZOBACTAM)

Susceptibilty (classification) ***Pathogen***	**Resistance rate**[a]
Susceptible (Gram-Positive Aerobes)	
Brevibacterium species*	
*Corynebacterium xerosis**	
Corynebacterium species	
Enterococcus durans	
*Enterococcus faecalis**	0 - 8 %
Enterococcus species*	0 - 4 %
*Gemella haemolysans**	
*Gemella morbillorum**	
*Lactococcus lactis cremoris**	
*Propionibacterium granulosum**	
Propionibacterium species	
*Staphylococcus aureus, methicillin-susceptible**	0 - 12 %
*Staphylococcus epidermidis**	0 - 25 %
*Staphylococcus haemolyticus**	
*Staphylococcus hominis**	
*Staphylococcus saprophyticus**	
*Staphylococcus sciuri**	

*Staphylococcus xylosus**	
Staphylococcus species, *coagulase negative**	
Streptococcus agalactiae	2 %
*Streptococcus anginosus**	
*Streptococcus beta hemolysans non group A**	
*Streptococcus beta hemolysans group D**	
*Streptococcus constellatus**	
*Streptococcus gordonii**	
*Streptococcus intermedius**	
*Streptococcus milleri**	
*Streptococcus milleri-group**	
*Streptococcus mitis**	
*Streptococcus morbillorum**	
*Streptococcus oralis**	
*Streptococcus pneumoniae**	0 - 2 %
*Streptococcus pyogenes**	0 - 3 %
*Streptococcus sanguis**	
*Streptococcus viridans**	
*Streptococcus viridans group**	0 - 17 %
Streptococcus species*	
Susceptible (Gram-Negative Aerobes)	
Acinetobacter anitratus	0 - 25 %
*Acinetobacter lwoffii**	0 - 4 %
*Aeromonas sobria**	
Alcaligenens species*	
Branhamella catarrhalis	
Burkholderia cepacia	0 - 30 %
Citrobacter diversus	9 %
*Citrobacter farmeri**	
*Citrobacter freundii**	0 - 25 %
Citrobacter koseri	
Citrobacter species*	
*Eikenella corrodens**	
Enterobacter agglomerans	17 %
*Enterobacter cloacae**	0 - 25 %
Enterobacter species	11 - 17 %
*Escherichia coli**	0 - 15 %
*Escherichia hermannii**	0 - 3 %
Escherichia vulneris	
*Haemophilus influenzae**	0 - 3 %
Haemophilus parainfluenzae	0 - 2 %
Haemophilus species	
*Klebsiella ornithinolytica**	
*Klebsiella oxytoca**	3 - 19 %
*Klebsiella pneumoniae**	3 - 17 %
Klebsiella species	0 - 18 %
Morganella morganii	0 - 5 %
*Pasteurella multocida**	
Proteus, indole positive	0 - 4 %
*Proteus mirabilis**	0 - 4 %
*Proteus vulgaris**	0 - 8 %
Proteus species*	
Providencia stuartii	11 %
Providencia species	2 %

*Pseudomonas aeruginosa**	0 - 29 %
Pseudomonas fluorescens	22 %
Pseudomonas putida	20 %
Pseudomonas species	2 - 30 %
Salmonella arizonae	
Salmonella species	0 - 3 %
Serratia liquefaciens	12 - 22 %
*Serratia marcescens**	0 - 38 %
*Serratia odorifera**	
Serratia species*	0 - 48 %
Shigella boydii	
Shigella dysenteriae	
Shigella flexneri	
Shigella sonnei	

Susceptible (Gram-Positive Anaerobes)

Bifidobacterium species*
*Clostridium bifermentans**
*Clostridium butyricum**
*Clostridium cadaveris**
*Clostridium clostridiforme**
*Clostridium difficile**
*Clostridium hastiforme**
*Clostridium limosum**
*Clostridium perfringens**
*Clostridium ramosum**
*Clostridium tertium**
Clostridium species*
Eubacterium aerofaciens
*Eubacterium lentum**
Eubacterium species
*Peptococcus asaccharolyticus**
Peptococcus species
*Peptostreptococcus anaerobius**
*Peptostreptococcus magnus**
*Peptostreptococcus micros**
*Peptostreptococcus prevotii**
Peptostreptococcus species*

Susceptible (Gram-Negative Anaerobes)

*Bacteroides caccae**	0 - 2 %
*Bacteroides capillosus**	
*Bacteroides distasonis**	
*Bacteroides fragilis**	0 - 3 %
Bacteroides fragilis group	
*Bacteroides ovatus**	0 - 15 %
*Bacteroides putredinis**	
*Bacteroides stercoris**	
*Bacteroides thetaiotaomicron**	
*Bacteroides uniformis**	
*Bacteroides ureolyticus**	
*Bacteroides vulgatus**	
Bacteroides species*	0 - 4 %
*Fusobacterium necrophorum**	
*Fusobacterium nucleatum**	
*Fusobacterium varium**	

Fusobacterium species*	
*Porphyromonas asaccharolytica**	
*Porphyromonas gingivalis**	
Porphyromonas species*	
Prevotella bivia	
*Prevotella disiens**	
*Prevotella intermedia**	
*Prevotella melaninogenica**	
*Prevotella oralis**	
Prevotella species*	
Intermediate Susceptible (Gram-Positive Aerobes)	
*Enterococcus avium**	15 - 45 %
*Enterococcus faecium**	15 - 93 %
*Propionibacterium acnes**	50 %
Intermediate Susceptible (Gram-Negative Aerobes)	
*Acinetobacter baumannii**	16 - 63 %
Acinetobacter calcoaceticus	30 - 58 %
Acinetobacter species*	0 - 75 %
Enterobacter aerogenes	7 - 79 %
*Pseudomonas stutzeri**	50 %
Stenotrophomonas maltophilia	1 - 53 %
Resistant (Gram-Positive Aerobes)	
Corynebacterium jeikeium	100 %
Staphylococcus aureus (methicillin resistant)	100 %
Staphylococcus coagulase negative (methicillin resistant)	100 %

[a] When no range is given this indicates that all isolates are susceptible; one percentage number (without any range) means that the organism was cited in one study.
* Clinical efficacy has been demonstrated for susceptible isolates in paediatric appendicitis complicated by rupture with peritonitis and/or abscess formation.

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 2g piperacillin /0.25g tazobactam to 4g piperacillin /0.5g tazobactam.

Both piperacillin and tazobactam are approximately 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.

TAZOCIN is widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite which has been found to be micro-biologically inactive.

Elimination

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

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

Following single or multiple doses of TAZOCIN 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

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

Haemodialysis removes 30% to 50% of TAZOCIN 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.

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.

5.3. Preclinical Safety Data

Preclinical mutagenicity and reproduction studies reveal no special hazards for humans.

Carcinogenicity studies have not been conducted with piperacillin, tazobactam, or the combination.

6. Pharmaceutical Particulars

6.1. List of Excipients

Citric Acid
Disodium edetate (dihydrate)(EDTA)

6.2. Incompatibilities

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 containing EDTA in vitro in certain diluents at specific concentrations. (See section 4.2 and 6.6)

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

TAZOCIN should be administered through an infusion set separately from any other drugs unless compatibility is proven.

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

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

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

6.3. Shelf Life

Unopened: 2 years

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4. Special Precautions for Storage

Do not store above 25°C. Keep vials in the outer carton in order to protect from light.

6.5. Nature and Contents of Container

TAZOCIN 2g/0.25g Powder for Solution for Injection or Infusion
Type I, 30ml glass vial with butyl rubber stopper and aluminium/plastic seal containing TAZOCIN 2g/0.25g of powder in an outer carton.

TAZOCIN 4g/0.5g Powder for Solution for Injection or Infusion
Type I, 70ml glass vial with butyl rubber stopper and aluminium/plastic seal containing TAZOCIN 4g/0.5g of powder in an outer carton.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.

Reconstitution Directions

Intravenous Injection

Each vial of TAZOCIN 2g/0.25g should be reconstituted with 10ml of one of the following diluents. Each vial of TAZOCIN 4g/0.5g should be reconstituted with 20ml of one of the diluents.

- Sterile Water for Injection
- 0.9% Sodium Chloride for Injection
- Dextrose 5%

Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 5-10 minutes.

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

Unused solution should be discarded.

Intravenous Infusion

Each vial of TAZOCIN 2g/0.25g should be reconstituted with 10ml of one of the diluents below. Each vial of TAZOCIN 4g/0.5g should be reconstituted with 20ml of one of the diluents below.

- Sterile Water for Injection
- 0.9% Sodium Chloride for Injection
- Dextrose 5%

The reconstituted solution should be further diluted to a minimum of 50ml and a maximum of 150ml with one of the following reconstitution diluents:

- 0.9% sodium chloride for injection
- Dextrose 5% in Water
- Hartmann's solution or Lactated Ringer's solution (compatible only with TAZOCIN containing EDTA)

If using the diluent Sterile Water for Injection the maximum recommended volume per dose is 50ml.

Tazocin product strength	Tazocin 2g/0.25g Initial reconstitution	Tazocin Final infusion volume	Tazocin final infusion concentration
2g/0.25g	10ml of Water for Injection or 0.9% Sodium Chloride for Injection or 5% Dextrose	50ml 100ml 150ml	45mg/ml 23mg/ml 15mg/ml
Infusion time: 20-30 minutes			

Tazocin product strength	Tazocin 4g/0.5g Initial reconstitution	Tazocin Final infusion volume	Tazocin final infusion concentration
4g/0.5g	20ml of water for injection or 0.9% Sodium Chloride for Injection or 5% Dextrose	50ml 100ml 150ml	90mg/ml 45mg/ml 30mg/ml
Infusion time: 20-30 minutes			

Unused solution should be discarded.

TAZOCIN should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Displacement Volume

Each gram of TAZOCIN lyophilised powder has a displacement volume of 0.7ml.

TAZOCIN 2g/0.25g will displace 1.58ml
TAZOCIN 4g/0.5g will displace 3.15ml

Co-administration with aminoglycosides

In circumstances where co-administration is thought essential, Tazocin containing EDTA in vials has been shown to be compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under certain conditions.

Tazocin can be co-administered via Y-site with either of the following aminoglycosides, please refer to the Summary of Product characteristics (SPC) of each respective product for full prescribing information:

AMIKACIN‡		
Final infusion concentration range (mg/ml)	Product strength (mg/ml)	Required Diluent volume*
1.75 – 7.5	250	143-33ml
INFUSION TIME: Please refer to the SPC for Amikacin		
GENTAMICIN‡		
Final infusion concentration range (mg/ml)	Product strength (mg/ml)	Required Diluent volume*
0.7 –3.32	40	57-12ml
INFUSION TIME: Please refer to the SPC for Gentamicin		

*** (0.9% Sodium Chloride)**

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

Simultaneous co-administration of an aminoglycoside and beta lactam is not recommended due to physical incompatibility. However when necessary simultaneous co-administration of Tazocin containing EDTA and the specific aminoglycoside, amikacin and gentamicin, in the manner described above is acceptable.

Guidance on checks that need to be performed by the Health Professionals when co-administering infusions:

1. **Strict asepsis** should be maintained throughout and in general the giving set should not be used for more than 24 hours.

2. The infusion container should be labelled with the patient's name, the name and quantity of additives, and the date and time of addition (including the new expiry date or time if applicable).

3. The intravenous infusion should be examined from time to time. If **cloudiness, crystallisation, change of colour**, or **any other sign of interaction** or **contamination** is observed the infusion should be discontinued.

7. Marketing Authorisation Holder

John Wyeth & Brother Limited
Trading as: Wyeth Pharmaceuticals
Huntercombe Lane South
Taplow,
Maidenhead,
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8. Marketing Authorisation Numbers

TAZOCIN 2g/0.25g Powder for solution for injection or infusion - PA 22/90/1
TAZOCIN 4g/0.5g Powder for solution for injection or infusion - PA 22/90/2

9. Date of First Authorisation/Renewal of Authorisation

Date of first authorisation: 22nd December 1992
Date of last renewal: 22nd December 2007

10. Date of Revision of the Text

Date of preparation: April 2009

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