



Public Assessment Report

from the Norwegian Medicines Agency

**Piperacillin/Tazobactam Stragen,
powder for solution for injection/infusion,
2 g/0.25 g and 4 g/0.5 g**

**Piperacillin
Tazobactam**

MA-holder: Stragen Nordic A/S, Denmark

MA-numbers in Norway:
06-4649 (2 g/0.25 g) and 06-4650 (4 g/0.5 g)

Date: 09-Oct-2009

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure
Module 2: Summary of product Characteristics (SPC)
Module 3: Package Leaflet

Module 1: Information about the initial procedure:

Type of application:	Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity, and also Article 10(3), hybrid application, due to differences in the indications or in the strengths.
Active substance:	Piperacillin and tazobactam
Pharmaceutical form:	Powder for solution for injection/infusion
Strengths:	2 g/0.25 g and 4 g/0.5 g
MA holder (in Norway):	Stragen Nordic A/S, Hesselvej 41, Ganløse, 3660 Stenløse, Denmark
Reference Member State:	Norway
Concerned Member States:	AT, BE, CZ, DE, DK, EL, FI, IE, LU, NL, PL, PT, SE, UK
Procedure Number:	NO/H/0121/001-002/DC
Timetable:	Start (Day 0): 06.06.2007 End (Day 210): 23.09.2008

Module 2: Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam Stragen 2 g/0.25 g, Powder for solution for injection or infusion
Piperacillin/Tazobactam Stragen 4 g/0.5 g, Powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 g piperacillin (as sodium salt) and 0.25 g tazobactam (as sodium salt).
One vial of powder for solution for injection or infusion contains 4.7 mmol (108 mg) of sodium.

Each vial contains 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt).
One vial of powder for solution for injection or infusion contains 9.4 mmol (216 mg) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
White to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/tazobactam is indicated for the treatment of moderate to severe systemic and/or local bacterial infections in which betalactamase producing bacteria are suspected or have been detected, such as:

Adults/Adolescents and the Elderly

Nosocomial pneumonia
Complicated urinary tract infections (including pyelonephritis)
Intra-abdominal infections
Skin and soft tissue infections
Bacterial infections in neutropenic adults

Children (2-12 years)

Bacterial infections in neutropenic children

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

4.2 Posology and method of administration

Piperacillin/tazobactam may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes).

For reconstitution instructions, see section 6.6.

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

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

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

Adults and children over 12 years, each with normal renal function

The usual dosage for adults and children over 12 years is piperacillin/tazobactam 4000/500 mg given every 8 hours.

The total daily dose of piperacillin/tazobactam depends on the severity and localisation of the infection and can vary from piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg administered every 6 or 8 hours.

In neutropenia the recommended dose is piperacillin/tazobactam 4000/500 mg given every 6 hours in combination with an aminoglycoside.

Elderly with normal renal function

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

Renal insufficiency in adults, the elderly and children (over 40 kg) receiving the adult dose

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

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

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

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

Children aged 2-12 years with normal renal function

Piperacillin/tazobactam is only recommended for the treatment of children with neutropenia.

Neutropenia

For children weighing less than 40 kg the dose should be adjusted to 90 mg/kg (piperacillin/tazobactam 80/10 mg) administered every 6 hours, in combination with an aminoglycoside, not exceeding Piperacillin/Tazobactam 4000/500 mg every 6 hours.

Renal insufficiency in children aged 2-12 years (or bodyweight less than 40 kg)

In children with renal insufficiency the intravenous dosage should be adjusted to the degree of actual renal impairment as follows:

Creatinine clearance (ml/min)	Recommended piperacillin/tazobactam dosage	Frequency	Maximum daily dosage
≥ 40	No adjustment necessary		

20-39	90 mg (piperacillin/tazobactam 80/10 mg) /kg	q 8H	12/1.5g/day
< 20	90 mg (piperacillin/tazobactam 80/10 mg) /kg	q 12H	8/1g/day

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

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

Children under 2 years

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

Hepatic impairment

No dose adjustment is necessary.

Duration of Therapy

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

In acute infections, treatment with Piperacillin/Tazobactam should be continued for 48 hours beyond the resolution of clinical symptoms or the fever.

4.3 Contraindications

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

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 piperacillin/tazobactam. 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 piperacillin/tazobactam, the antibiotic should be discontinued. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Before initiating therapy with piperacillin/tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporines, 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, piperacillin/tazobactam must be discontinued immediately in such cases, and suitable therapy should be initiated.

Precautions

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of a full blood count 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.

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

This medicinal product contains 2.4 mmol (54 mg) sodium per gram piperacillin. To be taken into account by patients on a controlled sodium diet.

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

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

Until further experience is available, piperacillin/tazobactam should not be used in children who do not have neutropenia.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with probenecid

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

Interaction with antibiotics

No clinically relevant adverse pharmacokinetic interaction with tobramycin or vancomycin has been observed in healthy adults with a normal renal function. The clearance of tobramycin and gentamicin was enhanced in patients with severe renal dysfunction using piperacillin/tazobactam. In these patients mixing of piperacillin/tazobactam formulation with tobramycin and gentamicin was excluded. For information related to the administration of piperacillin/tazobactam with aminoglycosides please refer to section 6.2.

Interaction with anticoagulants

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

Interaction with vecuronium

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the nondepolarising muscle relaxants could be prolonged in the presence of piperacillin. This should be taken into account when piperacillin/tazobactam is used peri-operatively.

Interaction with methotrexate

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

Interaction with laboratory test results

The administration of piperacillin/tazobactam may result in a false-positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reaction be used.

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

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies with piperacillin/tazobactam in combination or with piperacillin or tazobactam alone in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). Piperacillin and tazobactam cross the placenta. Piperacillin/tazobactam should only be used during pregnancy if clearly indicated.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, side effects may occur (see also 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed by frequency as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$); not known (cannot be estimated from the available data).

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

Body system	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Candidal superinfection
Blood and lymphatic system disorders	Uncommon	Leucopenia, neutropenia, thrombocytopenia
	Rare	Anaemia, 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	Very rare	Hypoalbuminaemia, hypoglycaemia,

disorders		hypoproteinaemia, hypokalaemia.
Nervous system disorders	Uncommon	Headache, insomnia
	Rare	Muscular weakness, hallucination, convulsion
Vascular disorders	Uncommon	Hypotension, phlebitis, thrombophlebitis
	Rare	Flushing
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomiting
	Uncommon	Constipation, dyspepsia, jaundice, stomatitis
	Rare	Abdominal pain, pseudomembranous colitis, dry mouth
Hepatobiliary disorders	Uncommon	Alanine aminotransferase increased, aspartate aminotransferase increased
	Rare	Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular 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

The administration of high doses of beta-lactams, particularly in patients with renal insufficiency, can lead to encephalopathies (consciousness fluctuation, myoclonus and convulsions).

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

4.9 Overdose

Symptoms

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

Treatment of intoxication

In the event of an overdose, piperacillin/tazobactam treatment should be discontinued.

No specific antidote is known.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Classification: J01CR05

Mechanism of action:

Piperacillin, a broad spectrum, semi-synthetic penicillin active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolymethyl penicillanic acid sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Mechanism of resistance:

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

Breakpoints:

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

EUCAST clinical MIC breakpoints 2008 (version 1.2):

Pathogen	Species-related breakpoints (S ≤ / R >) (For susceptibility testing the concentration of tazobactam is fixed at 4 mg/l)
<i>Enterobacteriaceae</i>	8/16
<i>Pseudomonas aeruginosa</i>	16/16
Gram-negative and Gram-	8/16

positive anaerobes	
<i>Staphylococcus</i> Methicillin-susceptible strains	S
Methicillin-resistant strains	R
Non-species related break-points	4/16

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

Commonly susceptible species

Gram positive aerobes

Brevibacterium spp
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus spp. methicillin-sensitive
Streptococcus pneumoniae
Streptococcus pyogenes
 Group B streptococci
*Streptococcus spp**

Gram negative aerobes

Branhamella catarrhalis
Citrobacter koseri
*Haemophilus influenzae**
Haemophilus spp.
Proteus mirabilis
Salmonella spp.
Shigella spp.

Gram positive anaerobes

Clostridium spp.
Eubacterium spp.
Peptococcus spp.
Peptostreptococcus spp.

Gram negative anaerobes

*Bacteroides fragilis**
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
*Prevotella spp**

Species for which resistance may be a problem

Gram positive aerobes

Staphylococcus aureus, methicillin-sensitive
Staphylococcus epidermis, methicillin-sensitive
Enterococcus avium (\$)
Enterococcus faecium (+ \$)
Propionibacterium acnes (\$)
Viridans streptococci

Gram negative aerobes

Actinobacter spp (+ \$)

Piperacillin/Tazobactam Stragen
 NO/H/0121/001-002/DC

Burkholderia cepacia
Citrobacter freundii
Enterobacter spp.
Escherichia coli *
Klebsiella spp.
Proteus, indole positive
*Pseudomonas aeruginosa**
Pseudomonas spp. *
Pseudomonas stutzeri \$
Serratia spp.

Gram negative anaerobes
Bacteroides spp. *

Inherently resistant organisms

Gram positive aerobes
Corynebacterium jeikeium
Staphylococcus spp. methicillin resistant

Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilia +\$

- * Clinical effectiveness against this has been demonstrated in the registered indications.
- (\$) Species showing natural intermediate susceptibility
- (+) Species for which high resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic properties

Distribution

Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion or injection. Piperacillin plasma levels produced when given with tazobactam are similar to those attained when equivalent doses of piperacillin are administered alone.

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

Both piperacillin and tazobactam are 20 to 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin/tazobactam is widely distributed in tissue and body fluids including intestinal mucosa, gall bladder, lung, bile and bone.

Biotransformation

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

Elimination

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

Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the

administered dose appearing as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

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

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

Impaired renal function

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

Impaired liver function:

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

Paediatric patients

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

Mean pharmacokinetic parameters of piperacillin/tazobactam of paediatric patients of different age groups.

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

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

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

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's solution is not compatible with piperacillin/tazobactam.

Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Unopened: 2 years

After reconstitution

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C.

After reconstitution and dilution:

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 48 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately.

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

6.4 Special precautions for storage

Do not store above 25° C.

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

6.5 Nature and contents of container

Type I glass vial (20 ml) with bromobutyl rubber stopper and aluminium cap with polypropylene flip-off system.

Type II glass vial (50 ml) with bromobutyl rubber stopper and aluminium cap with polypropylene flip-off system.

Pack size: 1 x 1 vial, 5 x 1 vial, 10 x 1 vial, 12 x 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution directions

Intravenous injection

Each vial of Piperacillin/Tazobactam Stragen 2 g/0.25 g powder for solution for injection or infusion should be reconstituted with 10 ml of one of the following diluents and

each vial of Piperacillin/Tazobactam Stragen 4 g/0.5 g powder for solution for injection or infusion should be reconstituted with 20 ml of one of the following diluents:

- Sterile water for injection
- 9 mg/ml (0.9%) sodium chloride for injection

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

Intravenous infusion:

Each vial of Piperacillin/Tazobactam Stragen 2 g/0.25 g powder for solution for injection or infusion should be reconstituted with 10 ml of one of the above diluents

each vial of Piperacillin/Tazobactam Stragen 4 g/0.5 g powder for solution for injection or infusion should be reconstituted with 20 ml of one of the above diluents.

The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents (maximum 50 ml, if diluted in sterile water for injection), or with Dextrose 5% in Water.

For single use only. Discard any unused solution.

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

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

7. MARKETING AUTHORISATION HOLDER

Stragen Nordic A/S
Hesselvej 41, Ganløse
3660 Stenløse
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Tel: +45 48 10 88 10
Fax: +45 48 10 88 11
email: Info@stragen.dk

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

28/09/2009

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Piperacillin/Tazobactam Stragen 2 g/0.25 g Powder for solution for injection/ infusion

Piperacillin/Tazobactam Stragen 4 g/0.5 g Powder for solution for injection / infusion

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.
- 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.

In this leaflet:

1. What Piperacillin/Tazobactam Stragen is and what it is used for
2. Before you are given Piperacillin/Tazobactam Stragen
3. How Piperacillin/Tazobactam Stragen is given
4. Possible side effects
5. How to store Piperacillin/Tazobactam Stragen
6. Further information

1. WHAT PIPERACILLIN/TAZOBACTAM STRAGEN IS AND WHAT IT IS USED FOR

Piperacillin belongs to the group of medicines called broad spectrum penicillin antibiotics, which can kill many types of bacteria. Tazobactam prevents some bacteria from resisting the effects of piperacillin. This means that when piperacillin and tazobactam are given together, more types of bacteria are killed.

Piperacillin/Tazobactam Stragen is used in adults to treat bacterial infections affecting your chest, urinary tract (kidneys and bladder), abdomen or skin.

Piperacillin/tazobactam Stragen is used in children aged 2-12 to treat bacterial infections in children with low white cell counts (reduced resistance to infections).

2. BEFORE YOU ARE GIVEN PIPERACILLIN/TAZOBACTAM STRAGEN

Do not use Piperacillin/Tazobactam Stragen

- if you are allergic (hypersensitive) to piperacillin, other antibiotics called penicillins or cephalosporins, tazobactam, or other medicines called beta-lactamase inhibitors.

Take special care with Piperacillin/Tazobactam Stragen

- if you have allergies. If you have several allergies make sure you tell your doctor or nurse before receiving this product
- if you are pregnant, think you may be pregnant, or are breast-feeding
- if you have low levels of potassium in your blood. Your doctor may want to 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 on a low sodium diet

Using other medicines

Please tell your doctor 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:

- Probenecid (for gout). 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 (for 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. water tablets, or some medicines for cancer).

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are trying for a baby, tell your doctor or nurse before receiving this product.

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

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed.

However, side effects could occur which may influence your ability to drive or use machines (see section 4).

Important information about some of the ingredients of this product

This medicinal product contains 4.7 mmol (108 mg) of sodium per vial (2 g /0.25 g) of powder for solution for injection or infusion.

This medicinal product contains 9.4 mmol (216 mg) of sodium per vial (4 g/ 0.5 g) of powder for solution for injection or infusion.

To be taken into consideration by patients on a controlled sodium diet.

3. HOW PIPERACILLIN/TAZOBACTAM STRAGEN IS GIVEN

Your doctor or nurse will give you this medicine by slow injection (for 3-5 minutes) or through a drip (for 20-30 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 children aged 2-12

The usual dose is 4g/0.5 g piperacillin/tazobactam given every 8 hours. Your doctor may reduce the dose depending on how serious your infection is.

If you are unable to fight infections normally, the usual dose is 4g/0.5 g piperacillin/tazobactam given every 6 hours at the same time as another antibiotic called an aminoglycoside, which is given into one of your veins. The two medicines should be given in separate syringes or drips.

In children, the doctor will calculate the dose depending on your child's weight.

You will be given Piperacillin/Tazobactam Stragen until the signs of infection have gone, and then, normally, for another 48 hours to make sure the infection has gone completely.

Children under 2 years of age

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

If you have kidney problems

Your doctor may need to reduce the dose of Piperacillin/Tazobactam Stragen 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 are given more Piperacillin/Tazobactam Stragen than you should

As you will be given Piperacillin/Tazobactam Stragen by a doctor or nurse, you are unlikely to be given the wrong dose. However, if you experience bad side effects or think you have been given too much, tell your doctor immediately.

If you miss a dose Piperacillin/Tazobactam Stragen

If you think you have not been given a dose of Piperacillin/Tazobactam Stragen, tell your doctor immediately.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Piperacillin/Tazobactam Stragen can cause side effects, although not everybody gets them.

If any of the following happens, stop taking Piperacillin/Tazobactam Stragen and tell your doctor or nurse immediately:

- Rare side effects (that affect less than 1 person in 1, 000):

Severe allergic reaction (sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat), bloody diarrhea.

- Very rare side effects (that affect less than 1 person in 10, 000):

Peeling and blistering of the skin, mouth, eye and genitals

The following side effects have also been reported:

Common side effects (affecting less than 1 in 10 patients but more than 1 in 100) are:

- diarrhoea
- nausea and vomiting
- skin rashes

Uncommon side effects (affecting less than 1 in 100 patients but more than 1 in 1000) are:

- thrush
- mild allergic reactions
- headache
- difficulty sleeping
- low blood pressure (felt as light-headedness)
- inflammation of the veins (felt as tenderness or redness in the affected area)
- constipation
- upset stomach
- jaundice (yellowing of the skin or whites of the eyes)
- mouth ulcers
- itching
- fever or hot flushes
- swelling or redness around the injection site
- changes in results of blood tests of kidney and liver function
- changes in the number of cells in the blood (red cells, white cells and platelets)

Rare side effects (affecting less than 1 in 1, 000 patients but more than 1 in 10,000) are:

- unusual bruising and bleeding
- weakness
- hallucinations (seeing or hearing things)
- convulsions or twitching
- dry mouth
- flushed red skin
- abdominal pain
- increased sweating
- eczema and other skin problems
- joint and muscle pain
- kidney problems
- tiredness
- water retention (seen as swollen hands, ankles or feet).

There have been very rare reports (in less than 1 in 10,000 patients) of:

- low blood glucose levels which may make you confused and shaky
- reduced blood concentration of potassium which can cause muscle weakness, twitching or abnormal heart rhythm.

Your doctor may want to perform tests during your treatment to measure any changes. 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 nurse.

5. HOW TO STORE PIPERACILLIN/TAZOBACTAM STRAGEN

Keep out of the reach and sight of children.

Do not use Piperacillin/Tazobactam Stragen after the expiry date which is stated on the vial label and carton. The expiry date refers to the last day of that month.

Powder:

Do not store above 25 °C.

Reconstituted/Diluted Product:

For storage conditions for the reconstituted/Diluted product see
"The following information is intended for medical or healthcare professionals only:"
at the end of the package leaflet.

6. FURTHER INFORMATION

What Piperacillin/Tazobactam Stragen contains

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).

There are no other ingredients.

What Piperacillin/Tazobactam Stragen looks like and contents of the pack

Piperacillin/Tazobactam Stragen is a white to off-white powder for solution for injection or infusion packaged in glass vials, packed in cartons containing 1, 5, 10 or 12 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Stragen Nordic A/S
Hesselvej 41, Ganløse
3660 Stenløse
Danmark
Tel: +45 48 10 88 10
Fax: +45 48 10 88 11
email: Info@stragen.dk

Marketing Authorisation Holder:

To be completed nationally

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

Manufacturer

<To be completed nationally>

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

[Name of Member States] [Name of the medicinal product]

[Name of Member States] [Name of the medicinal product]

This leaflet was last approved in 28/09/2009

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

Piperacillin/Tazobactam Stragen

Powder for solution for injection or infusion

This is an extract from the Summary of Product Characteristics to assist in the administration of Piperacillin/Tazobactam Stragen. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the SmPC.

For Slow Intravenous Injection and Slow Intravenous Infusion

Incompatibilities with diluents and other medicinal products

- Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam Stragen.
- When used concurrently with another antibiotic (e.g. aminoglycosides), Piperacillin/Tazobactam Stragen must be administered separately. Mixing with an aminoglycoside in vitro can cause inactivation of the aminoglycoside.
- Piperacillin/Tazobactam Stragen should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.
- Piperacillin/Tazobactam Stragen should be administered through an infusion set separately from any other drugs unless compatibility is proven.
- Due to chemical instability, Piperacillin/Tazobactam Stragen should not be used in solutions that contain sodium bicarbonate.
- Piperacillin/Tazobactam Stragen should not be added to blood products or albumin hydrolysates.

Reconstitution directions

Intravenous injection

Each vial of Piperacillin/Tazobactam Stragen 2 g/0.25 g powder for solution for injection or infusion should be reconstituted with 10 ml of one of the following diluents and each vial of Piperacillin/Tazobactam Stragen 4 g/0.5 g powder for solution for injection or infusion should be reconstituted with 20 ml of one of the following diluents:

- Sterile water for injection
- 9 mg/ml (0.9%) sodium chloride for injection

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

Intravenous infusion

Each vial of Piperacillin/Tazobactam Stragen 2 g/0.25 g powder for solution for injection or infusion should be reconstituted with 10 ml of one of the above diluents

each vial of Piperacillin/Tazobactam Stragen 4 g/0.5 g powder for solution for injection or infusion should be reconstituted with 20 ml of one of the above diluents.

The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents (maximum 50 ml, if diluted in sterile water for injection), or with Dextrose 5% in Water.

For single use only. Discard any unused solution.

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

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

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25° C.

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C.

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 48 hours when stored in a refrigerator at 2-8°C.

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

Module 4: Labelling

Not included

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Piperacillin/Tazobactam Stragen, 2 g /0.25 g and 4 g/0.5 g, powder for solution for injection/infusion. The procedure was finalised at 2008-09-16. For information on changes after this date please refer to the Annex 'Update'.

I. INTRODUCTION

Based on review of the submitted data, the Member States will grant a marketing authorisation (MA) for Piperacillin/Tazobactam Stragen, powder for solution for injection/infusion, 2 g/0.25 g and 4 g/0.5 g. The first date of authorisation in Norway was 2008-10-23. The product is approved for the following therapeutic indications:

Piperacillin/tazobactam is indicated for the treatment of moderate to severe systemic and/or local bacterial infections in which betalactamase producing bacteria are suspected or have been detected, such as:

Adults/Adolescents and the Elderly

Nosocomial pneumonia

Complicated urinary tract infections (including pyelonephritis)

Intra-abdominal infections

Skin and soft tissue infections

Bacterial infections in neutropenic adults

Children (2-12 years)

Bacterial infections in neutropenic children

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

A comprehensive description of the indications and the posology is given in the SPC (see Module 3).

The application was an abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic applications, and also Article 10(3) hybrid applications due to differences in the indications or in the strengths. The marketing authorisation in Norway is granted according to Article 10(3) of Directive 2001/83/EC as amended due to differences in the therapeutic indication for this medicinal product and the reference product.

This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological, non-clinical and clinical data. This information is not fully available in the public domain. Authorisations for generic medicinal products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired.

The reference product in the reference member state (RMS) is the innovator product Tazocin, marketed by Whyeth AB. Tazocin powder for solution for injection/infusion has been authorised in Norway since 1998-06-29.

II. QUALITY ASPECTS

II.1 Introduction

The drug product is a powder for solution for injection or infusion. It is packaged in glass vials. Following reconstitution with a suitable solvent in the glass vial, the solution is injected or further diluted with a suitable solvent. Please see SPC for further details.

II.2 Drug Substance

There are two drug substances in the drug product. These are Piperacillin and tazobactam. Both drug substances appear as their sodium salts in the formulation. Suitable specification has been presented for each of the drug substances, and their stability has been documented.

II.3 Medicinal Product

The drug product does not contain any excipients. The manufacturing process has been properly validated. Provided that the specific obligations agreed by the manufacturer are adequately resolved, the product specification includes suitable tests and requirements for the formulation type. The stability of the drug product during the established shelf life has been demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The reconstituted drug product is a sterile solution. Please see SPC for further details on dilution, in-use storage and handling of the reconstituted solution.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of piperacillin and tazobactam are well known. As piperacillin and tazobactam are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

The generic product Piperacillin/Tazobactam Stragen is a powder for solution for injection/ infusion and intended to be administered intravenously. It contains the same concentration of the same active substance (piperacillin/tazobactam) in the same pharmaceutical form as the currently authorised reference product in Norway (Tazocin «Wyeth AB»). A bioequivalence study is therefore not required, and Piperacillin/Tazobactam Stragen is considered essentially similar to Tazocin. The clinical efficacy and safety of the product can be referred to the reference product Tazocin which is approved with a full dossier,

The indications approved for the originator Tazocin show great diversity between the member states involved in this procedure. Thus, there were discussions about the indications which were divergent from those approved for the Norwegian originator. To support these divergent indications, the applicant submitted clinical documentation, i.e. scientific articles which describe double-blind, randomised and controlled clinical studies as well as other supportive clinical studies. Consequently, the following indications are considered adequately documented and approvable in addition to those previously approved for the Norwegian originator: “*Complicated urinary tract infections (including pyelonephritis)*”, “*Skin and soft tissue infections*” and “*Bacterial infections in neutropenic adults and children (2-12 years)*”.

IV.1 Discussion on the clinical aspects

This application concerns an abridged application for the generic product Piperacillin/Tazobactam Stragen. As explained above, this product is considered essentially similar to the reference product Tazocin. The efficacy and safety of the product can thus be referred to the reference product which is approved with a full dossier. Accordingly, the applicant is not required to provide results from non-clinical and clinical trials.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The reference product Tazocin, 2g/0.25 g and 4 g/0.5 g, powder for solution for injection/infusion has been marketed since 1998-06-29. Piperacillin/Tazobactam Stragen 2g/0.25 g and 4 g/0.5 g, powder for solution for injection/infusion is considered essentially similar to Tazocin. The efficacy and safety of the product can thus be referred to the original product which is approved with a full dossier. Consequently, benefit/risk ratio is considered positive for Piperacillin/Tazobactam Stragen and approval is recommended from clinical point of view.

From Quality point of view there are still some minor issues to be resolved. However, the RMS considers these to be adequately handled according to the list of commitments agreed by the Applicant.

For the time being, no EU-risk management plan is considered necessary for Piperacillin/Tazobactam Stragen. In order to address the compatibility issues between Piperacillin/ Tazobactam Stragen and the originator, the applicant commits to implement some follow-up measures.

Follow-up measures regarding agreed product information and information to health care professionals have been provided by the company.

Agreed Module 3 variations are to be submitted.

The SPC will be updated according to the harmonised SPC of the reference product Tazocin when available.