SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Yanoven 2 g + 0.25 g sterile powder for injectable solution for I.M./I.V.

Yanoven 4 g + 0.5 g sterile powder for solution for I.V. infusion

2. Qualitative and quantitative composition

Yanoven 2 g + 0.25 g sterile powder for injectable solution for I.M./I.V.

Each vial contains: Active ingredients: piperacillin sodium 2.085 g (equivalent to 2 g of piperacillin), tazobactam sodium 0.2683 g (equivalent to 0.25 g of tazobactam).

Each solvent ampoule contains: lidocaine hydrochloride 0.5%.

Yanoven 4 g + 0.5 g sterile powder for solution for I.V. infusion

Each vial contains: Active ingredients: piperacillin sodium 4.170 g (equivalent to 4 g of piperacillin), tazobactam sodium 0.5366 g (equivalent to 0.5 g of tazobactam).

3. Pharmaceutical form

Sterile powder for injectable solution I.M. / I.V.

Sterile powder for solution for I.V. infusion.

4. Clinical particulars

4.1. Therapeutic indications

Yanoven is a combination of piperacillin, a penicillin-class antibacterial and tazobactam, a betalactamase inhibitor, indicated for the treatment of:

• Intra-abdominal infections in adult and pediatric patients 2 months of

• age and older

• Nosocomial pneumonia in adult and pediatric patients 2 months of age

• and older

• Skin and skin structure infections in adults

• Female pelvic infections in adults

• Community-acquired pneumonia in adults

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Yanoven and other antibacterial drugs, YANOVEN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

4.2. Posology and method of administration

Dosage in Adult Patients with Indications Other Than Nosocomial Pneumonia:

The usual total daily dosage of piperacillin and tazobactam for injection for adult patients with indications other than nosocomial pneumonia is 3.375 g every six hours [totaling 13.5 g (12 g piperacillin and 1.5 g tazobactam)], to be administered by intravenous infusion over 30 minutes. The usual duration of piperacillin and tazobactam for injection treatment is from 7 to 10 days.

Dosage in Adult Patients with Nosocomial Pneumonia:

Initial presumptive treatment of adult patients with nosocomial pneumonia should start with piperacillin and tazobactam for injection at a dosage of 4.5 g every six hours plus an aminoglycoside, [totaling 18 g (16 g piperacillin and 2 g tazobactam)], administered by intravenous infusion over 30 minutes. The recommended duration of piperacillin and tazobactam for injection treatment for nosocomial pneumonia is 7 to 14 days. Treatment with the aminoglycoside should be continued in patients from whom P. aeruginosais isolated.

Dosage in Adult Patients with Renal Impairment:

In adult patients with renal impairment (creatinine clearance ≤ 40 mL/min) and dialysis patients (hemodialysis and CAPD), the intravenous dose of piperacillin and tazobactam for injection should be reduced based on the degree of renal impairment. The recommended daily dosage of piperacillin and tazobactam for injection for patients with renal impairment administered by intravenous infusion over 30 minutes is described in the following table:

Creatinine Clearance (ml/min)	All indications (Except nosocomial pneumonia)	Nosocomial Pneumonia
Greater than 40 mL/min	3.375 every 6 hours	4.5 every 6 hours
20 to 40 mL/min*	2.25 every 6 hours	3.375 every 6 hours
Less than 20 mL/min*	2.25 every 8 hours	2.25 every 6 hours
Hemodialysis**	2.25 every 12 hours	2.25 every 8 hours
CAPD	2.25 every 12 hours	2.25 every 8 hours

Administer piperacillin and tazobactam for injection by intravenous infusion over 30 minutes.

* Creatinine clearance for patients not receiving hemodialysis

** 0.75 g (0.67 g piperacillin and 0.08 g tazobactam) should be administered following each hemodialysis session on hemodialysis days.

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g piperacillin and tazobactam for injection (0.67 g piperacillin and 0.08 g tazobactam) should be administered following each dialysis period on hemodialysis days. No additional dosage of piperacillin and tazobactam for injection is necessary for CAPD patients.

Dosage in Pediatric Patients with Appendicitis/Peritonitis or Nosocomial Pneumonia:

The recommended dosage for pediatric patients with appendicitis and/or peritonitis or nosocomial pneumonia aged 2 months of age and older, weighing up to 40 kg, and with normal renal function, is described in the following table:

Age	Appendicitis and/or Peritonitis	Nosocomial Pneumonia
2 months to 9 months	90 mg/kg (80 mg piperacillin and 10 mg tazobactam) every 8 hours	90 mg/kg (80 mg piperacillin and 10 mg tazobactam) every 6 hours
Older than 9 months of age	112.5 mg/kg (100 mg piperacillin and 12.5 mg tazobactam) every 8 hours	112.5 mg/kg (100 mg piperacillin and 12.5 mg tazobactam) every 6 hours

Administer piperacillin and tazobactam for injection by intravenous infusion over 30 minutes. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose.

Dosage of piperacillin and tazobactam for injection in pediatric patients with renal impairment has not been determined.

Duration of Therapy

For acute infections, therapy would last for a minimum of 5 days and a maximum of 14 days, and should be continued for another 48 hours after resolution of clinical symptoms or fever.

4.3. Contraindications

Piperacillin and tazobactam for injection is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors.

4.4. Special warnings and precautions for use

Hypersensitivity Adverse Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions (including shock) have been reported in patients receiving therapy with piperacillin and tazobactam for injection. These reactions are more likely to occur in individuals with a history of penicillin, cephalosporin, or carbapenem hypersensitivity or a history of sensitivity to multiple allergens. Before initiating therapy with piperacillin and tazobactam for injection, careful inquiry should be made concerning previous hypersensitivity reactions. If an allergic reaction occurs, piperacillin and tazobactam for injection should be discontinued and appropriate therapy instituted.

Severe Cutaneous Adverse Reactions

Piperacillin and tazobactam for injection may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis.

If patients develop a skin rash they should be monitored closely and Piperacillin and tazobactam for injection discontinued if lesions progress.

Hemophagocytic Lymphohistiocytosis

Cases of hemophagocytic lymphohistiocytosis (HLH) have been reported in pediatric and adult patients treated with piperacillin and tazobactam for injection. Signs and symptoms of HLH may include fever, rash, lymphadenopathy, hepatosplenomegaly and cytopenia. If HLH is suspected, discontinue piperacillin and tazobactam for injection immediately and institute appropriate management.

Hematologic Adverse Reactions

Bleeding manifestations have occurred in some patients receiving beta-lactam drugs, including piperacillin. 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, piperacillin and tazobactam for injection should be discontinued and appropriate therapy instituted.

The leukopenia/neutropenia associated with piperacillin and tazobactam for injection administration appears to be reversible and most frequently associated with prolonged administration.

Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, i.e., ≥ 21 days.

Central Nervous System Adverse Reactions

As with other penicillins, piperacillin and tazobactam for injection may cause neuromuscular excitability or seizures.

Patients receiving higher doses, especially patients with renal impairment may be at greater risk for central nervous system adverse reactions. Closely monitor patients with renal impairment or seizure disorders for signs and symptoms of neuromuscular excitability or seizures.

Nephrotoxicity in Critically Ill Patients

The use of piperacillin and tazobactam for injection was found to be an independent risk factor for renal failure and was associated with delayed recovery of renal function as compared to other betalactam antibacterial drugs in a randomized, multicenter, controlled trial in critically ill patients. Based on this study, alternative treatment options should be considered in the critically ill population. If alternative treatment options are inadequate or unavailable, monitor renal function during treatment with piperacillin and tazobactam for injection.

Combined use of piperacillin and tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury.

Electrolyte Effects

Yanoven contains 2.35 mEq (54 mg) of sodium per gram of piperacillin. This should be considered when treating patients requiring restricted salt intake.

Periodic electrolyte determinations should be performed in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Clostridioides difficile -Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including piperacillin and tazobactam for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of

C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria

Prescribing piperacillin and tazobactam for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

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.

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 substance are unaffected.

Aminoglycosides

Piperacillin, either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.

The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see section 4.4). Some of these studies have reported that the interaction is vancomycin dose-dependent.

No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Piperacillin Sodium and Tazobactam Sodium for Injection 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 PlateliaAspergillus EIA tests may lead to false-positive results for patients receiving Piperacillin Sodium and Tazobactam Sodium for Injection.

Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with

Bio-Rad Laboratories PlateliaAspergillus EIA test have been reported.

Positive test results for the assays listed above in patients receiving Piperacillin

Sodium and Tazobactam Sodium for Injection should be confirmed by other diagnostic methods.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of Piperacillin Sodium and

Tazobactam Sodium for Injection 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 following are clinically significant adverse reactions:

- Hypersensitivity Adverse Reactions
- Severe Cutaneous Adverse Reactions
- Hemophagocytic Lymphohistiocytosis
- Rhabdomyolysis
- Hematologic Adverse Reactions
- Central Nervous System Adverse Reactions
- Nephrotoxicity in Critically Ill Patients
- Clostridioides difficile-Associated Diarrhea

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Patients

During the initial clinical investigations, 2621 patients worldwide were treated with Piperacillin/Tazobactam in phase 3 trials. In the key North American monotherapy clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, Piperacillin/Tazobactam was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse Reactions from Piperacillin/Tazobactam Monotherapy Clinical Trials

System Organ Class Adverse Reaction
Gastrointestinal disorders Diarrhea (11.3%)
Constipation (7.7%) Nausea (6.9%) Vomiting (3.3%) Dyspepsia (3.3%) Abdominal pain (1.3%)
General disorders and administration site conditions Fever (2.4%) Injection site reaction (≤1%) Rigors (≤1%)
Immune system disorders Anaphylaxis (≤1%)
Infections and infestations Candidiasis (1.6%) Pseudomembranous colitis (≤1%)
Metabolism and nutrition disorders Hypoglycemia (≤1%)
Musculoskeletal and connective tissue disorders Myalgia (≤1%) Arthralgia (≤1%)
Nervous system disorders Headache (7.7%)
Psychiatric disorders Insomnia (6.6%)
Skin and subcutaneous tissue disorders Rash (4.2%, including maculopapular, bullous, and urticarial) Pruritus (3.1%) Purpura (≤1%)
Vascular disorders Phlebitis (1.3%) Thrombophlebitis (≤1%) Hypotension (≤1%) Flushing (≤1%)
Respiratory, thoracic and mediastinal disorders Epistaxis (≤1%)

Nosocomial Pneumonia Trials

Two trials of nosocomial lower respiratory tract infections were conducted. In one study, 222 patients were treated with Piperacillin/Tazobactam in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with imipenem/cilastatin (500 mg/500 mg every 6 hours) in combination with an aminoglycoside. In this trial, treatmentemergent adverse events were reported by 402 patients, 204 (91.9%) in the piperacillin

and tazobactam group and 198 (92.1%) in the imipenem/cilastatin group. Twenty-five (11.0%) patients in the piperacillin and tazobactam group and 14 (6.5%) in the imipenem/cilastatin group ($p > 0.05$) discontinued treatment due to an adverse event.

The second trial used a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside.

Adverse Reactions from Piperacillin/Tazobactam Plus Aminoglycoside Clinical Trials

Blood and lymphatic system disorders
Thrombocythemia (1.4%)
Anemia (≤1%)
Thrombocytopenia (≤1%)
Eosinophilia (≤1%)

Gastrointestinal disorders
Diarrhea (20%)
Constipation (8.4%)
Nausea (5.8%)
Vomiting (2.7%)
Dyspepsia (1.9%)
Abdominal pain (1.8%)
Stomatitis (≤1%)

General disorders and administration site conditions
Fever (3.2%)
Injection site reaction (≤1%)

Infections and infestations
Oral candidiasis (3.9%)
Candidiasis (1.8%)

Investigations
BUN increased (1.8%)
Blood creatinine increased (1.8%)
Liver function test abnormal (1.4%)
Alkaline phosphatase increased (≤1%)
Aspartate aminotransferase increased (≤1%)
Alanine aminotransferase increased (≤1%)

Metabolism and nutrition disorders

Hypoglycemia (≤1%)
Hypokalemia (≤1%)

Nervous system disorders
Headache (4.5%)

Psychiatric disorders
Insomnia (4.5%)

Renal and urinary disorders
Renal failure (≤1%)

Skin and subcutaneous tissue disorders
Rash (3.9%)
Pruritus (3.2%)

Vascular disorders
Thrombophlebitis (1.3%)
Hypotension (1.3%)

Other Trials: Nephrotoxicity

In a randomized, multicenter, controlled trial in 1200 adult critically ill patients, piperacillin and tazobactam was found to be a risk factor for renal failure (odds ratio 1.7, 95% CI 1.18 to 2.43), and associated with delayed recovery of renal function as compared to other beta-lactam antibacterial drugs.

Adverse Laboratory Changes (Seen During Clinical Trials)

Of the trials reported, including that of nosocomial lower respiratory tract infections in which a higher dose of Piperacillin/Tazobactam was used in combination with an aminoglycoside, changes in laboratory parameters include:

• Hematologic—decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet

• count, eosinophilia, leukopenia, neutropenia. These patients were withdrawn from therapy; some

• had accompanying systemic symptoms (e.g., fever, rigors, chills)

• Coagulation—positive direct Coombs' test, prolonged prothrombin time, prolonged partial

• thromboplastin time

• Hepatic—transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin

• Renal—increases in serum creatinine, blood urea nitrogen

• Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in

• sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood

• glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time

• prolonged.

Clinical Trials in Pediatric Patients

Clinical studies of Piperacillin/Tazobactam in pediatric patients suggest a similar safety profile to that seen in adults.

In a prospective, randomized, comparative, open-label clinical trial of pediatric patients, 2 to 12 years of age, with intra-abdominal infections (including appendicitis and/or peritonitis), 273 patients were treated with Piperacillin/Tazobactam 112.5 mg/kg given IV every 8 hours and 269 patients were treated with cefotaxime (50 mg/kg) plus metronidazole (7.5 mg/kg) every 8 hours. In this trial, treatment-emergent adverse events were reported by 146 patients, 73 (26.7%) in the Piperacillin/Tazobactam group and 73 (27.1%) in the cefotaxime/metronidazole group. Six patients (2.2%) in the

Piperacillin/Tazobactam group and 5 patients (1.9%) in the cefotaxime/metronidazole group discontinued due to an adverse event.

In a retrospective, cohort study, 140 pediatric patients 2 months to less than 18 years of age with nosocomial pneumonia were treated with Piperacillin/Tazobactam and 267 patients were treated with comparators (which included ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin). The rates of serious adverse reactions were generally similar between the

Piperacillin/Tazobactam and comparator groups, including patients aged 2 months to 9 months treated with Piperacillin/Tazobactam 90 mg/kg IV every 6 hours and patients older than 9 months and less than 18 years of age treated with Piperacillin/Tazobactam 112.5 mg/kg IV every 6 hours.

Postmarketing Experience

In addition to the adverse drug reactions identified in clinical trials, the following adverse reactions have been identified during post-approval use of Piperacillin/Tazobactam. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Hepatobiliary—hepatitis, jaundice

• Hematologic—hemolytic anemia, agranulocytosis, pancytopenia

• Immune—hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock), hemophagocytic lymphohistiocytosis (HLH), acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.

• Renal—interstitial nephritis

• Nervous system disorders—seizures

• Psychiatric disorders—delirium

• Respiratory—eosinophilic pneumonia

• Skin and Appendages—erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, (DRESS), acute generalized exanthematous pustulosis (AGEP), dermatitis exfoliative, and linear IgA bullous dermatosis.

• Musculoskeletal Disorders—rhabdomyolysis

Postmarketing experience with Piperacillin/Tazobactam in pediatric patients suggests a similar safety profile to that seen in adults.

Reporting of suspected adverse reactions

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9. Overdose

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

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 hemodialysis. Following a single 3.375 g dose of piperacillin and tazobactam, the percentage of the piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively.

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 cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / 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 (EUCAST Clinical Breakpoint Table Version 10.0, valid from 2020-01-01). For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.

Pathogen	**Species-related breakpoints (S≤/R>), mg/L of piperacillin**
Enterobacterales (formerly *Enterobacteriaceae*)	8/16
Pseudomonas aeruginosa	<0.001/16[1]
Staphylococcus species	-[2]
Enterococcus species	-[3]
Streptococcus Groups A, B, C, and G	-[4]
Streptococcus pneumoniae	-[5]
Viridans group streptococci	-[6]
Haemophilus influenzae	0.25/0.25
Moraxella catarrhalis	-[7]
Gram-positive anaerobes (except *Clostridioides difficile*)	8/16
Gram-negative anaerobes	8/16
Non-species related (PK/PD) breakpoints	4/16

[1]For several agents, EUCAST has introduced breakpoints which categorise wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)". Susceptible breakpoints for these organism-agent combinations are listed as arbitrary, "off scale" breakpoints of S ≤ 0.001 mg/L.

[2]Most staphylococci are penicillinase producers, and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to

achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins. Ampicillin susceptibleS. saprophyticusaremecA-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[3]Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon inE. faecalis(confirm with MIC) but common inE. faecium.

[4]The susceptibility ofStreptococcusgroups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for Streptococcus group B. Streptococcus groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit. [5]The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude betalactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). Streptococcus pneumoniado not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit. Susceptibility inferred from ampicillin (MIC or zone diameter).

[6]For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin. [7]Susceptibility can be inferred from amoxicillin-clavulanic acid.

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(ampicillin- or penicillin-susceptible isolates only)
Listeria monocytogenes
Staphylococcus aureus(methicillin-susceptible isolates only)
Staphylococcus species, *coagulase negative* (methicillin-susceptible isolates only)
Streptococcus agalactiae(Group B streptococci)[†] *Streptococcus pyogenes*(Group A streptococci)[†]
Aerobic Gram-negative micro-organisms

Citrobacterkoseri
Haemophilusinfluenzae
Moraxella catarrhalis
Proteus mirabilis
Anaerobic Gram-positive micro-organisms
Clostridium species
*Eubacterium*species
Anaerobic gram-positive cocci††
Anaerobic Gram-negative micro-organisms
*Bacteroidesfragilis*group
*Fusobacterium*species
*Porphyromonas*species
*Prevotella*species
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecium
Streptococcus pneumoniae†
Streptococcus viridans group†
Aerobic Gram-negative micro-organisms
Acinetobacterbaumannii
Citrobacterfreundii
*Enterobacter*species
Escherichia coli
Klebsiellapneumoniae
Morganellamorganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
*Serratia*species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Corynebacteriumjeikeium
Aerobic Gram-negative micro-organisms
Burkholderiacepacia *Legionella* species *Ochrobactrumanthropi*

Stenotrophomonasmaltophilia
Other micro-organisms
Chlamydophilapneumoniae
Mycoplasma pneumoniae
†Streptococci are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in penicillin-binding proteins (PBPs) and, therefore, susceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in*S. pyogenes*. ††Including *Anaerococcus*, *Finegoldia*, *Parvimonas*, *Peptoniphilus*, and *Peptostreptococcus* spp.

Merino Trial (blood stream infections due to ESBL producers)

In a prospective, non-inferiority, parallel-group, published randomized clinical trial, definitive (i.e. based on susceptibility confirmed in-vitro) treatment with piperacillin/tazobactam, compared with meropenem, did not result in a non-inferior 30-day mortality in adult patients with ceftriaxone-non-susceptible E. coli or K.

pneumonia blood stream infections.

A total of 23 of 187 patients (12.3%) randomized to piperacillin/tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI − ∞ to 14.5%]; P = 0.90 for non-inferiority). The difference did not meet the non-inferiority margin of 5%.

Effects were consistent in an analysis of the per-protocol population, with 18 of 170 patients (10.6%) meeting the primary outcome in a piperacillin/tazobactam group compared with 7 of 186 (3.8%) in the meropenem group (risk difference, 6.8%

[one-sided 97.5% CI, - ∞ to 12.8%]; P = 0.76 for non-inferiority).

Clinical and microbiological resolution (secondary outcomes) by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, 6.2% [95% CI − 15.5 to 3.1%]; P = 0.19). For secondary outcomes, statistical tests were 2-sided, with a P

<0.05 considered significant.

In this trial, a mortality imbalance between study groups was found. It was supposed that deaths occurred in piperacillin/tazobactam group were related to underlying diseases rather than to the concomitant infection.

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 / tazobactamis 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 desethylpiperacillin 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

Nonclinical Toxicology:

Non-clinical 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

None

6.2. Incompatibilities

Whenever Yanoven is to be administered together with other antibiotics (for example aminoglycosides), the drugs should be administered separately. The in vitro admixture of Yanoven with an aminoglycoside may cause substantial deactivation of the action of the aminoglycoside. However it has been demonstrated that amikacin and gentamicin are compatible in vitro with Yanoven in certain diluents at specific concentrations, but only for simultaneous Y-site infusion. In the case of intramuscular administration, piperacillin / tazobactam and aminoglycosides should be reconstituted and administered separately in different injection sites.

Yanoven should not be mixed with other drugs in the same syringe or infusion bottle, since compatibility has not been established.

Yanoven should not be used with solutions containing sodium bicarbonate alone because of its chemical instability.

Yanoven should not be added to haematic products or to albumin hydrolysates.

6.3. Shelf life

Unopened: 36 months.

After reconstitution using the appropriate solvent, the solutions for intravenous and intramuscular use are stable for 24 hours if stored at room temperature and for 48 hours if refrigerated (2 - 8°C). Unused solutions must be discarded.

6.4. Special precautions for storage

See the expiry date printed on the outer carton.

This date refers to the product stored correctly in unopened package.

Beware not to use Yanoven after this date.

Store below 30°C.

6.5. Nature and contents of container

Yanoven 2 g + 0.25 g sterile powder for injectable solution I.M. / I.V.

Pack of 1 powder vial of 2 g + 0.25 g of piperacillin and tazobactam and one 4ml solvent ampoule of 0.5% lidocaine hydrochloride or pack of 10 vials.

20 ml Type III glass vial with a bromobutyl rubber type I.

Yanoven 2 g + 0.25 g sterile powder for solution for I.V. infusion

1 powder vial of 2 g + 0.25 g of piperacillin and tazobactam 20 ml Type III glass vial with a bromobutyl rubber type I.

Yanoven 4 g + 0.5 g sterile powder for solution for I.V. infusion

1 or 10 powder vials of 4 g + 0.5 g of piperacillin and tazobactam.

50 ml Type II glass vial with a bromobutyl rubber type I.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

A. Intramuscular administration

Yanoven 2 g + 0.25 g must be reconstituted using lidocaine hydrochloride 0.5 % solvent included in the packaging.

Lidocaine solvent ampoule is for intramuscular use only.

Do not exceed the dosage of 2 g + 0.25 g of piperacillin/tazobactam per injection site.

Do not administer Yanoven 4 g + 0.5 g by intramuscular injection.


Pic. 1


Pic. 2

Follow the instructions for reconstitution indicated below:

1) Shake the powder vial until the powder is detached from the bottom of the vial.

2) Remove the plastic cap to expose the central portion of rubber stopper and keep it (Pic. 1).

Avoid touching the central portion of rubber stopper.

3) Draw the lidocaine hydrochloride solvent into the syringe and inject it into the powder vial.

4) Cover the rubber stopper with the plastic cap to avoid touching with the fingers its central portion. Shake until the powder is completely dissolved. Shaking constantly, the reconstitution should take place within 10 minutes (Pic. 2).

5) Keep the solution aside until the foam disappears and a clear solution is obtained.

6) Remove the plastic cap and draw the solution into a 5 ml syringe for intramuscular administration.

B.Intravenous administration

Yanoven 2 g / 0.25 g and Yanoven 4 g / 0.5 g will be given by infusion over a period of at least 30 minutes.

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).

Vial content (piperacillin / tazobactam)	Quantity of solvent* to be added
Yanoven 2 g + 0.25 g	10 ml
Yanoven 4 g + 0.5 g	20 ml

*Compatible solvents for reconstitution:

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

- Sterile water for injections

- Glucose 5%

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labeled amount of piperacillin and tazobactam.The reconstituted solutions should be further diluted (recommended volume per dose of 50 ml to 150 ml) with one of the following compatible solvents:

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

- Glucose 5%

Co-administration of piperacillin/tazobactam with aminoglycosides

Considering the inactivation in vitro of the aminoglycosides by the beta-lactamic antibiotics, the separate administration of piperacillin/tazobactam and of the aminoglycosides is recommended. If a concomitant therapy with aminoglycosides should be considered appropriate, the piperacillin/tazobactam and the aminoglycosides should be reconstituted, diluted and administered separately.

In the case of administration intramuscularly, piperacillin / tazobactam and the aminoglycosides should be reconstituted and administered separately in different injection sites.

In circumstances where co-administration is recommended, piperacillin/tazobactam is compatible for simultaneous co-administration via

Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Piperacillin/ Tazobactam Dose (g)	Diluent volume (ml)	Aminoglycoside concentration range* (mg/ml)	Acceptable diluents
Amikacin	2.25 g 4.5 g	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2.25 g 4.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

*The dose of aminoglycosides should be calculated considering the patient's weight, the state of the infection (serious or endangering life) and kidney function (creatinine clearance). The concentration ranges in the table above are based on administration of the aminoglycoside in divided doses (10 -15 mg/kg/day in two daily doses for amikacin and 3-5 mg/kg/day in three daily doses for gentamicin).

Compatibility of piperacillin/tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dose of piperacillin/tazobactam listed in the above table have been established as compatible for coadministration 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 piperacillin/tazobactam.

7. MARKETING AUTHORISATION HOLDER

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Jadra Alchouf, Mount Lebanon,

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