SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Yanoven 2 g + 0.25 g sterile powder and solvent for I.M. injectable solution

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 and solvent for I.M. injectable solution

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%, water for injection.

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).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile powder and solvent for I.M. injectable solution.

Sterile powder for solution for I.V. infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Adults and adolescents

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

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

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

Note: Use for bacteraemia due to extended-beta-lactamase (ESBL) producing E. coli and K. pneumoniae (ceftriaxone non-susceptible), is not recommended in adult patients, see section

5.1.

Children 2 to 12 years of age

- Complicated intra-abdominal infections
Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

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

4.2 Posology and method of administration

Posology

The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

Infections

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

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	Piperacillin/Tazobactam 4 g / 0.5 g
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Patients with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

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

Patients with hepatic impairment

No dose adjustment is necessary (see section 5.2).

Elderly patients

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

Paediatric population (2-12 years of age)

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	Indication / condition
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

* Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.

Pateints with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
> 50	No dose adjustment needed.
≤ 50	70 mg piperacillin / 8.75 mg tazobactam / kg every hours.

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam / kg should be administered following each dialysis period.

Use in children aged below 2 years

The safety and efficacy of Piperacillin/Tazobactam in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Method of administration

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients listed in section 6.1.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

4.4 Special warnings and precautions for use

The selection of piperacillin / tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.

Before initiating therapy with Piperacillin/Tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in

patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

Piperacillin/Tazobactam 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 (see section 4.8). If patients develop a skin rash they should be monitored closely and piperacillin / tazobactam discontinued if lesions progress.

Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin/Tazobactam, should be discontinued.

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

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

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

As with treatment with other penicillins, neurological complications in the form of convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

Piperacillin/Tazobactam 2 g / 0.25 g contains 108 mg of sodium per vial equivalent to 5.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This should be taken into consideration for patients who are on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

Renal Impairment

Due to its potential nephrotoxicity (see section 4.8), piperacillin/tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment (see section 4.2).

In a secondary analysis using data from a large multicenter, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported in patients treated with piperacillin/tazobactam, often following treatment longer than 10 days. HLH is a life-threatening syndrome of pathologic immune activation 6haracterized by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, piperacillin/Tazobactam treatment should be discontinued.

Rhabdomyolysis has been reported with the use of Piperacillin/Tazobactam. If signs or symptoms of rhabdomyolysis are observed, Piperacillin/Tazobactam should be discontinued and appropriate therapy initiated.

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 mechanism 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 substances are unaffected.

Aminoglycosides

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

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

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

Vancomycin

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/Tazobactam therapy.

A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dip sticks is not affected.

The direct Coombs test may be positive.

Bio-Rad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving Piperacillin/Tazobactam. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Positive test results for the assays listed above in patients receiving Piperacillin/Tazobactam should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation Pregnancy

Pregnancy

There are no or a limited amount of data from the use of Piperacillin/Tazobactam 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 effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported adverse reactions is diarrhea (occurring in patient out of 10).

Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

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

System Organ Class	Very common (≥1/10)	Common (>1/100 to <1/10)	Uncommon (>1/1,000 to <1/100)	Rare (>1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from the available data)
Infections and infestations		Candida infection*		Pseudomembranous colitis	
Blood and lymphatic system disorders		Thrombocytopenia, anaemia*	Leukopenia	Agranulocytosis	Pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*, eosinophilia*
Cardiac disorders					Kounis syndrome*, **
Immune system disorders					Anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*

System Organ Class	Very common (≥1/10)	Common (>1/100 to <1/10)	Uncommon (>1/1,000 to <1/100)	Rare (>1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			Hypokalaemia		
Psychiatric disorders		Insomnia			Delirium*
Nervous system disorders		Headache	Seizure*		
Vascular disorders			Hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				Epistaxis	Eosinophilic pneumonia
Gastrointestinal disorders	Diarrhoea	Abdominal pain, vomiting, constipation, nausea, dyspepsia		Stomatitis	
Hepatobiliary disorders					Hepatitis*, jaundice
Skin and subcutaneous tissue disorders		Rash, pruritus	Erythema multiforme*, urticaria, rash maculopapular*	Toxic epidermal necrolysis*	Stevens-Johnson syndrome*, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS), *acute generalized exanthematous pustulosis* (AGEP)*, dermatitis bullous, linear IgA disease*, purpura
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia		rhabdomyolysis
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*
		Pyrexia, injection site reaction	Chills		
Investigations		alanine aminotransferase increased, aspartate aminotransferase	blood glucose decreased, blood bilirubin increased, prothrombin		bleeding time prolonged, gammaglutamyltransferase increased

System Organ Class	Very common (≥1/10)	Common (>1/100 to <1/10)	Uncommon (>1/1,000 to <1/100)	Rare (>1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from the available data)
		increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged	time prolonged		

*ADR identified post marketing

**Acute coronary syndrome associated with an allergic reaction

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

Beta-lactam antibiotic class effects

Beta-lactam antibiotics, including piperacillin tazobactam, may lead to manifestations of encephalopathy and convulsions (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

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

Treatment

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

No specific antidote is known.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, combinations of penicillins, including beta-lactamase inhibitors

ATC code: J01CR05

Mechanism of action:

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

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

Phamacokinetic / Pharmacodynamic relationship:

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

Mechanism of resistance

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

• Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular classes B, C and D.

• 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 12.0, valid from 2022-01-01). **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*)	8/8
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]
Bacteroides species (except *B. thetaiotaomicron*)	8/8
Prevotella species	0.5/0.5
Fusobacterium necrophorum	0.5/0.5
Clostridium perfringens	0.5/0.5
Cutibacterium acnes	0.25/0.25
Achromobacter xylosoxidans	4/4
Vibrio species	1/1
Non-species related (PK/PD) breakpoints	8/16

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 susceptible S. saprophyticus are mecA-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 in E. faecalis (confirm with MIC) but common in E. faecium.

4 The susceptibility of Streptococcus groups 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 beta-lactam 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 pneumoniae do 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

Citrobacter koseri

Haemophilus influenza

Moraxella catarrhalis

Proteus mirabilis

Anaerobic Gram-positive micro-organisms

Clostridium species

Eubacterium species

Anaerobic gram-positive cocci††

Anaerobic Gram-negative micro-organisms

Bacteroides fragilis group

Fusobacterium species

Porphyromonas species

Prevotella species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive micro-organisms

Enterococcus faecium

Streptococcus pneumoniae†

Streptococcus viridans group†

Aerobic Gram-negative micro-organisms

Acinetobacter baumannii

Citrobacter freundii

Enterobacter species

Escherichia coli

Klebsiella pneumonia

Morganella morganii

Proteus vulgaris

Providencia ssp.

Pseudomonas aeruginosa

Serratia species

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive micro-organisms

Corynebacterium jeikeium

Aerobic Gram-negative micro-organisms

Burkholderia cepacia

Legionella species

Ochrobactrum anthropi

Stenotrophomonas maltophilia

Other microorganisms

Chlamydophilia pneumonia

Mycoplasma pneumonia

† 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. pneumoniae 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 and tazobactam is widely distributed in tissue and body fluids including intestinal mucosa, gall bladder, 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 micro-biologically inactive.

Elimination

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

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

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

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

Special populations

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

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

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

Paediatric population

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

Elderly patients

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

Race

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

5.3 Preclinical safety data

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 pup mortality, increase in stillbirths) 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

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 with solutions that contain sodium bicarbonate.

Lactated Ringer's (Hartmann´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: 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).

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 and solvent for I.M. injectable solution
1 powder vial of 2 g + 0.25 g of piperacillin and tazobactam and 1 solvent ampoule of 20 mg/ 4 ml of lidocaine hydrochloride.

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 powder vial of 4 g + 0.5 g of piperacillin and tazobactam.
50 ml Type II glass vial with a bromobutyl rubber type I.

6.6 Special precautions for disposal and other handling

No special requirements.

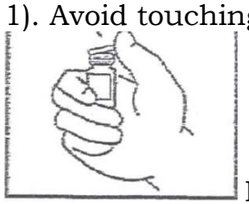
The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Instructions for reconstitution and dilution

A. Intramuscular administration

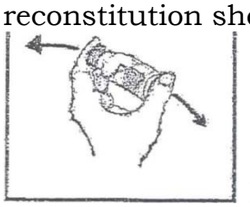
Yanoven 2 g + 0.25 g must be reconstituted using lidocaine hydrochloride 0.5 % solvent included in the packaging.
The solvent with lidocaine is for intramuscular use only.
Do not exceed the dosage of 2 g + 0.25 g of piperacillin/tazobactam per injection site. Do not administer Yanoven 4 g + 0.5 g by intramuscular injection.
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 cap.


Pic. 1

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).


Pic. 2

5) Keep the solution aside until the foam disappears and a clear solution is obtained.
6) Remove the rubber cap and draw the solution into a 5 ml syringe for intramuscular administration.

B. Intravenous administration

To be administered only by healthcare professionals.

Intravenous administration

Reconstitute the product with the quantity of solvent indicated in the following table, using one of the compatible solutions listed below. Shake until completely dissolved. Shaking constantly, the reconstitutions should take place within 10 minutes.

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 solutions

- Water for injection
- Saline solution
- Saline solution with benzyl alcohol
- Saline solution with parabens
- Dextrose 5 %

Shake the powder vial until the powder is detached from the bottom of the vial.
Draw one of the solvents indicated above into the syringe and inject it into the powder vial.
Shake until the powder is completely dissolved.
Shaking constantly, the reconstitution should take place within 10 minutes.
Keep the solution aside until the foam disappears and a clear solution is obtained. Before drawing the reconstituted solution into the syringe, ensure that the powder is completely dissolved.

7) If reconstitution has been carried out as described, the solution in the syringe shall contain the quantity of piperacillin and tazobactam declared on the label. The reconstituted solution can be further diluted to the required volume (50-150 ml) using a compatible intravenous diluents solution listed below:

- Water for injection (The maximum recommended volume of water for injection is 50 ml per dose).
- Saline solution
- Glucose solution 5%
- Dextran 6% in saline solution

7. MARKETING AUTHORISATION HOLDER

ARWAN Pharmaceutical Industries Lebanon s.a.l. Jadra, Lebanon

Manufactured at –

LABORATORY & ALLIED LTD Address: PLOT NO: 209/10349 OFF MOMBASA ROAD,
P.O BOX 42875, CODE 00100 NAIROBI
Country: KENYA
Telephone: + 254 – 20-8040306
Telefax: 254 – 020 - 8040309
E-Mail: info@laballied.com

8. MARKETING AUTHORISATION NUMBER(S) –

Yanoven 2.25g: H2021/CTD8138/15319
Yanoven 4.5g: H2021/CTD8193/16141

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--

10th Dec 2021

10. DATE OF REVISION OF THE TEXT

December 2026