SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TAVOCTAME 4g/0.5g powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
One vial of Tavoctame 4g/0.5g powder for solution for infusion contains 9.4 mmol (216 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TAVOCTAME 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.

TAVOCTAME 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

TAVOCTAME 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 TAVOCTAME 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 eight hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every six 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	**TAVOCTAME 4 g / 0.5 g**
Every six hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial

	infection.
Every eight hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

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

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

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

Hepatic Impairment
No dose adjustment is necessary (see section 5.2).

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

Paediatric population (2-12 years of age)

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

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

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

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

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

TAVOCTAME 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For reconstitution instructions, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients 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 TAVOCTAME, 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.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis have been reported in patients receiving TAVOCTAME (see section 4.8). If patients develop a skin rash they should be monitored closely and TAVOCTAME discontinued if lesions progress.

Haemophagocytic lympohistiocytosis (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 characterised 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.

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 TAVOCTAME, should be discontinued.

Therapy with TAVOCTAME 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 a full blood count should be performed.

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

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), TAVOCTAME 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 TAVOCTAME was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that TAVOCTAME 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).

TAVOCTAME contains sodium
Each vial of TAVOCTAME 4g/0.5g contains 9.4 mmol (216 mg) of sodium To be taken into account by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Methotrexate
Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.

Probenecid
As with other penicillins, concurrent administration of probenecid and piperacillin/tazobactam produces a longer half-life and lower renal clearance

for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

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

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

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

Vancomycin
No pharmacokinetic interactions have been noted between Piperacillin/ Tazobactam and vancomycin.
However, a limited number of retrospective 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.

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 TAVOCTAME 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 TAVOCTAME. 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 TAVOCTAME 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 TAVOCTAME 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. TAVOCTAME 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 breast 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 reaction is diarrhoea (occurring in 1 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 available data)**
Infections and infestations		candidiasis*		pseudo-membranous	

				colitis	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*	leukopenia,	agranulocytosis,	Pancytopenia*, neutropenia, haemolytic anaemia*, eosinophilia*, thrombocytosis*
Immune system disorders					anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia,		
Psychiatric disorders		insomnia			delirium*
Nervous system disorders		headache, insomnia	seizure*		
Vascular disorders			hypotension, thrombophlebitis, phlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, nausea, constipation, 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

					generalised exanthematous pustulosis (AGEP)*, dermatitis bullous purpura
Musculoskeletal and connective tissue disorders			arthralgia, myalgia		
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*
General disorders and administration site conditions		pyrexia, injection site reaction	chills		
Investigations		alanine aminotransferase increased, aspartate aminotransferase 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	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gamma-glutamyltransferase increased

*ADR identified post marketing

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: 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.

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 TAVOCTAME 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 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

Gram positive aerobes
Enterococcus faecalis (ampicillin- or penicillin-susceptible isolates only)
Listeria monocytogenes
Staphylococcus aureus, methicillin susceptible£
Staphylococcus species, coagulase negative, methicillin-susceptible
Streptococcus pyogenes (Group A streptococci)
Streptococcus agalactiae (Group B streptococci)

Gram negative aerobes
Citrobacter koseri
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis

Gram positive anaerobes
Clostridium spp.
Eubacterium spp.
Anaerobic gram-positive cocci
Peptostreptococcus spp.

Gram negative anaerobes
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.

Species for which acquired resistance may be a problem

Gram positive aerobes
Enterococcus faecium $,.+
Streptococcus pneumoniae
Streptococcus viridans group

Gram negative aerobes
Actinobacter baumannii $
Burkholderia cepacia
Citrobacter freundii
Enterobacter spp.
Escherichia coli
Klebsiella pneumonia
Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia spp.

Inherently resistant organisms

Gram positive aerobes
Corynebacterium jeikeium

Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilia +,$
Burkholderia cepacia
Ochrobactrum anthropi

Other microorganisms
Chlamydophilia pneumonia
Mycoplasma pneumonia

$ *Species showing natural intermediate susceptibility*
+ *Species for which high resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU.*
£ *All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.*

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/Tazobactam is widely distributed in tissue 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, 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 clearance of tazobactam.

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

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

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

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

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

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

5.3 Preclinical safety data

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

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination Piperacillin/Tazobactam reported a decrease in the number of births 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) concurrently 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 TAVOCTAME is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of TAVOCTAME with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

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

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

TAVOCTAME should not be added to blood products or albumin hydrolysates

6.3 Shelf life

Unopened - 3 years

Reconstituted solutions will remain stable for 12 hours at temperature 2-8°C, when the reconstitution is made with one of the compatible solutions referred to paragraph 6.6.

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

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Glass vial with rubber stopper and flip-off aluminium cap, which is contained in a cartoon box.

Pack sizes: 1 and 10 vials.

6.6 Special precautions for disposal

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.

Intravenous use
Each vial content should be reconstituted with the volume of solvent shown in the table below, using one of the compatible solutions for reconstitution. Shake well until it dissolves. With constant shaking, reconstitution should generally be achieved within 5 to 10 minutes (for details of handling, please see below).

Vial content	Volume of solution* which should be added into the vial
4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)	20 ml

Compatible solutions for reconstitution
Sodium chloride 0.9% (9 mg/ml)
Sterile water for injections [(1)]
Glucose 5%
[(1)] The maximum recommended volume of sterile water for injections per dose is 50 ml.

Reconstituted solutions should be taken from the vial with a syringe. After reconstitution according to the instructions, the contents of the vial taken with a syringe will provide the indicated amount of Piperacillin and Tazobactam.

The reconstituted solutions should be further diluted to the preferable volume (50ml to 150ml) with one of the following diluents
- Sodium chloride 0.9% (9 mg/ml)
- Dextrose 5%.

Co-administration with Aminoglycosides
Due to the in vitro hibernation of aminoglycosides from β lactamine antibiotics, it is proposed separate administration of Tavoctame and aminoglycosides. Tavoctame and aminoglycoside should be reconstituted and diluted separately when there is an indication for concomitant treatment with aminoglycosides. In cases where co-administration is recommended, Tavoctame is compatible for simultaneous concomitant use by infusion via a triple lumen (Y-site) catheter with only the following aminoglycosides and under the following conditions:

Aminoglycoside	TAVOCTAMEDose	TAVOCTAME Solvent volume (ml)	Aminoglycoside Concentration Range* (mg/ml)	Acceptable solvents/solutions
Amikacin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	1.75 – 7.5	Sodium chloride 0.9% or Dextrose 5%
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	Sodium chloride 0.9% or Dextrose 5%

* The dose of aminoglycosides should be based on the patient's weight, the condition of the infection (severe or life-threatening) and renal function (creatinine clearance).

The compatibility of TAVOCTAME with other aminoglycosides has not been established. Only the concentration and dilution means for amiodarone and gentamicin with the doses of TAVOCTAME, as listed in the table above have been shown to be compatible for concomitant infusion via a triple lumen (Y-

site) catheter. Simultaneous concomitant administration by infusion via a triple lumen catheter (Y-site) in any way other than the one mentioned above can lead to inactivation of the aminoglycoside from TAVOCTAME. See. Paragraph 6.2 for incompatibilities.

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

For single use only. Discard any solution that was not used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 55461/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2024

10 DATE OF REVISION OF THE TEXT

22/02/2024