SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TIPRAXIN 2 g/0.25 g Lyophilized Powder for Solution for IV Injection/Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: Each vial contains,
Sodium piperacillin 2,085 g (equivalent to 2 g of piperacillin)
Sodium tazobactam 0,268 g (equivalent to 0.25 g of tazobactam)

Excipients:
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder
The vials contain a white or almost white sterile powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults and children aged 12 years and older
TIPRAXIN;

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

It is also indicated for the treatment of bacteremia associated or potentially associated with the infections mentioned above.

TIPRAXIN can be used in the treatment of febrile neutropenic patients with suspected bacterial infection.

In children aged 2-12 years

- Complicated intraabdominal infections

TIPRAXIN can be used for the treatment of febrile neutropenic pediatric patients with suspected bacterial infection.
Official guidelines regarding the appropriate use of antibacterial agents should be considered.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The total daily dose and frequency of TIPRAXIN depend on the infection site, severity, and the type of pathogen.

In adults and children aged 12 years and older, the general dose is 4 g/0.5 g of TIPRAXIN every 8 hours.

For neutropenic patients with nosocomial pneumonia and bacterial infections, the recommended dose is 4 g/0.5 g of TIPRAXIN every 6 hours.

This regimen can also be used for the treatment of other severe infections where TIPRAXIN is indicated.

The following table shows the recommended frequency and dosage based on symptoms for adult and pediatric patients aged 12 years and older:

Treatment frequency	**TIPRAXIN 4 g/0.5 g**
Every 6 hours	Severe pneumonia
	Febrile neutropenic adult patients with suspected bacterial infection
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Complicated skin and soft tissue infections (including diabetic foot infections)

For pediatric patients aged 2-12 years
The following table shows the recommended frequency and dosage based on weight for pediatric patients aged 2-12 years:

Dosage based on weight and treatment	Symptoms
Every 6 hours per kg, 80 mg piperacillin / 10 mg tazobactam	Febrile neutropenic pediatric patients with suspected bacterial infection*
Every 8 hours per kg, 100 mg piperacillin / 12.5 mg tazobactam	Complicated intra-abdominal infections*

*The maximum dose should not exceed 4 g/0.5 g for at least 30 minutes.

Treatment duration

For most indications, the general treatment duration ranges from 5 to 14 days. However, the treatment duration should be guided by the severity of the infection, the pathogens, and the patient's clinical/bacteriological progress.

Method of administration:
TIPRAXIN should be administered by slow intravenous injection (3-5 minutes) or infusion (20-30 minutes).
For dilution instructions before administration, see Section 6.6.

Additional information on special populations:
Renal impairment:
In adults and children aged 12 years and older with renal insufficiency, the intravenous dose should be adjusted according to the degree of renal impairment as follows (each patient should be closely monitored for signs of toxicity; the dose and frequency of administration should be adjusted accordingly):

Creatinine clearance (mL/min)	**TIPRAXIN (recommended dose)**
> 40	No dose adjustment required
20-40	Maximum recommended dose: 4 g/0.5 g every 8 hours
< 20	Maximum recommended dose: 4 g/0.5 g every 12 hours

In hemodialysis patients, since hemodialysis removes 30-50% of piperacillin within 4 hours, a supplemental dose of 2 g/250 mg TIPRAXIN should be given after each dialysis session.
For pediatric patients aged 2-12 years with renal insufficiency, the intravenous dose should be adjusted according to the degree of renal impairment as follows (each patient should be closely monitored for signs of toxicity; the dose and frequency of administration should be adjusted accordingly):

Creatinine clearance (mL/min)	**TIPRAXIN (recommended dose)**
> 50	No dose adjustment required
≤ 50	70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours

For pediatric patients undergoing hemodialysis, a supplemental dose of 40 mg piperacillin/5 mg tazobactam/kg TIPRAXIN should be given after each dialysis session.
Hepatic impairment

In patients with hepatic impairment, no dosage adjustment is necessary.

Pediatric population
The safety and efficacy of TIPRAXIN have not been established in patients under 2 years of age.

No controlled clinical trial data is available.

Geriatric population
TIPRAXIN can be administered at the same dose levels as adults, except in cases of renal impairment.

4.3 Contraindications
TIPRAXIN use,

- in patients who are hypersensitive to the active substance, any other penicillin-type antibacterial agents, or any excipients
- It is contraindicated in patients with a history of acute severe allergic reactions to beta-lactam active substances (including cephalosporins, monobactams, and carbapenems).

4.4 Special warnings and precautions for use
When deciding to initiate TIPRAXIN therapy, the appropriateness of using a broad-spectrum semi-synthetic penicillin should be evaluated based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.

Before starting treatment with TIPRAXIN, previous hypersensitivity reactions to penicillins, other beta-lactam agents (cephalosporins, monobactams, or carbapenems), and other allergens should be carefully investigated. Some patients with a history of multiple allergies have reported serious, sometimes fatal, hypersensitivity reactions (anaphylactic/anaphylactoid [including shock]) during treatment with penicillins, including piperacillin/tazobactam. If a serious hypersensitivity reaction occurs during TIPRAXIN therapy, the antibiotic should be discontinued. Severe anaphylactic reactions may require epinephrine or other emergency measures.

Serious skin reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) (see Section 4.8), have been reported in patients receiving piperacillin/tazobactam. If a rash develops, the patient should be closely monitored, and if the lesions progress, TIPRAXIN should be discontinued.

Antibiotic-induced pseudomembranous colitis can manifest as severe, persistent diarrhea that can be life-threatening. Symptoms of pseudomembranous colitis may begin during or after antibacterial treatment. In this case, TIPRAXIN should be discontinued.

Treatment with TIPRAXIN may lead to the emergence of resistant organisms that can cause superinfection.

Some patients using beta-lactam antibiotics have experienced bleeding events. These reactions are often associated with alterations in coagulation tests such as clotting time, platelet aggregation, and prothrombin time, and are more commonly seen in patients with renal insufficiency. If bleeding events occur as a result of antibiotic treatment, the antibiotic should be discontinued, and appropriate treatment should be initiated.

Leukopenia and neutropenia may develop, particularly during prolonged treatment. Therefore, periodic hematological monitoring is recommended.

As with other treatments with penicillins, especially in patients with impaired renal function, neurological attacks (seizures) may occur when high doses are administered (see Section 4.8).

In patients with low potassium reserves or those receiving medicinal products that can lower potassium levels, hypokalemia may develop. Regular monitoring of electrolytes may be recommended for these patients.

Renal impairment

Due to the nephrotoxic potential (see Section 4.8), piperacillin/tazobactam should be used cautiously in patients with renal insufficiency or those undergoing hemodialysis. The intravenous dose and frequency of administration should be adjusted based on the degree of renal impairment (see Section 4.2).

In a secondary analysis of data from a multicenter, randomized controlled trial, the glomerular filtration rate (GFR) was examined in critically ill patients treated with commonly used antibiotics. Treatment with piperacillin/tazobactam was associated with a lower reversible GFR compared to other antibiotics. The secondary analysis concluded that piperacillin/tazobactam led to delayed renal recovery in patients.

Combination therapy with piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute renal failure (see Section 4.5).

Due to the active ingredients piperacillin sodium and tazobactam sodium, this medicinal product contains 4.7 mmol (108 mg) of sodium per vial, which is equivalent to 5.4% of the maximum recommended daily intake of 2 g of sodium for adults, according to the WHO.

4.5 Interaction with other medicinal products and other forms of interaction

Non-depolarizing muscle relaxants
It is believed that piperacillin plays a role in prolonging the neuromuscular blockade of vecuronium when used concurrently. Due to similar mechanisms of action, the neuromuscular blockade caused by any non-depolarizing muscle relaxant is expected to be prolonged in the presence of piperacillin.

Anticoagulants
During concomitant treatment with heparin, oral anticoagulants, and other drugs that affect the coagulation system, including platelet function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Methotrexate
Piperacillin may reduce the excretion of methotrexate; therefore, serum methotrexate levels should be monitored to prevent drug toxicity.

Probenesid
As with other penicillins, the concurrent use of probenecid and TIPRAXIN results in a longer half-life and reduced renal clearance of piperacillin and tazobactam. However, the plasma peak concentrations of both drugs remain unaffected.

Aminoglycosides
Piperacillin, either alone or in combination with tazobactam, does not significantly alter the pharmacokinetics of tobramycin in individuals with normal renal function or mild-to-moderate renal insufficiency. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite are also not significantly affected by tobramycin administration. The inactivation of tobramycin and gentamicin by piperacillin has been observed in patients with severe renal insufficiency.

For information on the administration of piperacillin/tazobactam with aminoglycosides, please see Sections 6.2 and 6.6.

Vancomycin
Studies have shown that combination therapy with piperacillin/tazobactam and vancomycin leads to an increased incidence of acute kidney injury compared to vancomycin alone (see Section 4.4). Some of these studies have reported that the interaction is dose-dependent on vancomycin.

There is no pharmacokinetic interaction between piperacillin/tazobactam and vancomycin.

Effects on laboratory tests

As with other penicillins, non-enzymatic methods for measuring urinary glucose may lead to false-positive results. Therefore, enzymatic urinary glucose measurements are required during TIPRAXIN treatment.

Chemical methods used for measuring protein in urine may lead to false-positive results. Protein measurement with test strips is not affected.

The direct Coombs test may be positive.

In patients receiving piperacillin/tazobactam, the Bio-Rad Laboratories *Platelia Aspergillus* EIA test may lead to false-positive results. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses have been reported with the Bio-Rad Laboratories *Platelia Aspergillus* EIA test.

Positive test results for the tests listed above in patients receiving TIPRAXIN should be confirmed by other diagnostic methods.

Additional information for special populations
There are no interaction studies available for special populations.

Pediatric population
There are no interaction studies available for the pediatric population.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category: B

Women of childbearing potential / Contraception in males and females:
There is insufficient data.

Pregnancy:
There are no sufficient studies regarding the use of TIPRAXIN during pregnancy.

Studies in animals have shown developmental toxicity at maternally toxic doses, but no evidence of teratogenicity (see Section 5.3).

Piperacillin and tazobactam cross the placenta. It should be used in pregnant women only if the therapeutic benefit to the mother outweighs the potential risks to the patient and fetus.

Animal studies do not show direct or indirect harmful effects on pregnancy, embryonic/fetal development, birth, or postnatal development (see Section 5.3).

Caution should be exercised when administering to pregnant women.

Lactation:
Piperacillin excreted in breast milk at low concentrations. There has been no study regarding the concentration of tazobactam in breast milk. In breastfeeding women, it should only be used if the therapeutic benefit to the mother outweighs the risks to the patient and baby.

Fertility:
A fertility study in rats showed no effects on fertility or mating following intraperitoneal administration of tazobactam or the piperacillin/tazobactam combination (see Section 5.3).

4.7 Effects on ability to drive and use machines
No studies have been conducted on the ability to drive or use machines.

4.8 Undesirable effects
The most frequently reported side effect is diarrhea (observed in 1 in 10 patients). The most serious side effects include pseudomembranous colitis and toxic epidermal necrolysis, which occur in 1 to 10 out of every 10,000 patients. The frequency of pancytopenia, anaphylactic shock, and Stevens-Johnson syndrome cannot be predicted based on available data.

The following undesirable effects are listed according to organ system class and preferred terms according to MedDRA. Undesirable effects are ranked in decreasing severity within each frequency group.

Undesirable effects are categorized as follows: 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); Very rare (<1/10,000); Unknown (cannot be estimated from the available data).

Infections and infestations
Common: Candidiasis*
Rare: Pseudomembranous colitis

Blood and lymphatic system disorders
Common: Thrombocytopenia, anemia*
Uncommon: Leukopenia
Rare: Agranulocytosis
Unknown: Pancytopenia*, neutropenia, hemolytic anemia*, thrombocytosis*, eosinophilia*

Immune system disorders

Unknown: Anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*

Metabolism and nutrition disorders
Uncommon: Hypokalemia

Psychiatric disorders
Common: Insomnia
Unknown: Delirium*

Nervous system disorders
Common: Headache
Uncommon: Seizure*

Vascular disorders
Uncommon: Hypotension, thrombophlebitis, phlebitis, hot flushes

Respiratory, thoracic, and mediastinal disorders
Rare: Epistaxis
Unknown: Eosinophilic pneumonia

Gastrointestinal disorders
Very common: Diarrhea
Common: Abdominal pain, nausea, vomiting, constipation, dyspepsia
Rare: Stomatitis

Hepatobiliary disorders
Unknown: Hepatitis*, jaundice

Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Erythema multiforme*, urticaria, maculopapular rash*
Rare: Toxic epidermal necrolysis*
Unknown: Stevens-Johnson syndrome*, exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), bullous dermatitis, purpura

Musculoskeletal, connective tissue, and bone disorders
Uncommon: Arthralgia, myalgia

Kidney and urinary tract disorders
Unknown: Kidney failure, tubulointerstitial nephritis*

General disorders and administration site conditions
Common: Fever, injection site reactions
Uncommon: Tremor
Investigations
Common: Increased alanine aminotransferase, increased aspartate aminotransferase, decreased total protein in blood, decreased albumin in blood, positive direct Coombs test, increased creatinine in blood, increased alkaline phosphatase in blood, increased urea in blood, prolonged activated partial thromboplastin time
Uncommon: Decreased blood glucose, increased bilirubin in blood, prolonged prothrombin time
Unknown: Prolonged bleeding time, increased gamma-glutamyl transferase

*Post-marketing detected side effects

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

Beta-lactam Antibiotic Class Effects
Beta-lactam antibiotics, including piperacillin-tazobactam, may cause symptoms of encephalopathy and convulsions (see Section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose
Symptoms
After the product was marketed, overdose incidents related to piperacillin/tazobactam have been reported. These incidents, which included symptoms such as nausea, vomiting, and diarrhea, were mostly reported even with the usual recommended doses. If doses higher than recommended are administered intravenously, patients may experience neuromuscular excitability or convulsions (especially in the presence of renal insufficiency).

Treatment

In the case of overdose, piperacillin/tazobactam treatment should be discontinued. No known antidote exists. Symptomatic and supportive treatment should be applied based on the patient's clinical condition.

Excessive concentrations of piperacillin or tazobactam in the serum can be reduced through hemodialysis (see Section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Penicillin combinations with beta-lactamase inhibitors
ATC code: J01CR05

Mechanism of Action:

Piperacillin, a broad-spectrum semi-synthetic penicillin, exhibits bactericidal activity by inhibiting both septum formation and cell wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases that cause widespread 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 developed resistance to piperacillin.

Pharmacokinetic/Pharmacodynamic Relationship:
The duration above the minimum inhibitory concentration (T>MIC) is considered the major pharmacodynamic determinant of effectiveness for piperacillin.

Mechanism of Resistance:
The two main resistance mechanisms against piperacillin/tazobactam are:

- Inactivation of the piperacillin component by beta-lactamases that are not inhibited by tazobactam: Beta-lactamases in molecular classes B, C, and D. Furthermore, tazobactam does not provide protection against extended-spectrum beta-lactamases in molecular classes A and D.
- Modification of penicillin-binding proteins (PBPs), which leads to a reduction in the affinity of piperacillin for the molecular target.

Additionally, changes in bacterial membrane permeability, as well as the expression of multidrug efflux pumps, particularly in Gram-negative bacteria, can contribute to or cause bacterial resistance to piperacillin/tazobactam.

Breakpoints

EUCAST Clinical MIC Breakpoints for piperacillin/tazobactam (EUCAST Clinical Breakpoints Table Version 10.0, valid from: 01.01.2020). For susceptibility testing purposes, the tazobactam concentration is fixed at 4 mg/L.

Pathogen	Non-species-specific breakpoints (S≤/R>), mg/L piperacillin
*Enterobacterales (*formerly known as *Enterobacteriaceae)*	8/16
Pseudomonas aeruginosa	<0,001/16[1]
Staphylococcus species	-[2]
Enterococcus species	-[3]
Streptococcus Group 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 (excluding *Clostridioides difficile*)	8/16
Gram-negative anaerobes	8/16
Non-species-specific (PK/PD) Breakpoints	4/16

[1] For various drugs, EUCAST has introduced breakpoints that categorize wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the drug) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)." For these organism-drug combinations, susceptible breakpoints are listed as discretionary, "non-scaled" breakpoints of S≤0.001 mg/L.

[2] Most staphylococci are penicillinase producers, and some are methicillin-resistant. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin, and ticarcillin. Staphylococci tested for susceptibility to benzylpenicillin and cefoxitin can be reported as susceptible to all penicillins. Staphylococci resistant to benzylpenicillin but tested for cefoxitin susceptibility are susceptible to β-lactamase inhibitor combinations, isoxazolyl penicillins (oxacillin, cloxacillin, and flucloxacillin), and nafcillin. For orally administered drugs, ensuring adequate exposure at the site of infection is essential. Staphylococci tested and found resistant to cefoxitin are resistant to all penicillins. Ampicillin-susceptible *S. saprophyticus* is mecA-negative and is susceptible to ampicillin, amoxicillin, and piperacillin (with or without a β-lactamase inhibitor).

[3] Susceptibility to ampicillin, amoxicillin, and piperacillin (with or without a β-lactamase inhibitor) can be inferred from ampicillin susceptibility. Ampicillin resistance is uncommon in *E. faecalis* (confirmed by MIC) but is common in *E. faecium.*

[4] The susceptibility of *Streptococcus* groups A, B, C, and G to penicillins is inferred from benzylpenicillin susceptibility, except for group B *Streptococcus*, for which phenoxymethylpenicillin and isoxazolyl penicillins should be considered. *Streptococcus* groups A, B, C, and G do not produce β-lactamase. Therefore, the addition of a β-lactamase inhibitor does not provide a clinical benefit.

[5] To exclude β-lactam resistance mechanisms, either the oxacillin 1 µg disk screening test or a benzylpenicillin MIC test will be used. If screening is negative (oxacillin inhibition zone ≥20 mm or benzylpenicillin MIC ≤0.06 mg/L), all β-lactam drugs with available clinical breakpoints—including those listed under "Note"—can be reported as susceptible without additional testing, except for cefaclor, which should be reported as "susceptible, increased exposure (I). *Streptococcus pneumoniae* does not produce β-lactamase. The addition of a β-lactamase inhibitor does not provide a clinical benefit. Susceptibility can be inferred from ampicillin (MIC or zone diameter).

[6] For benzylpenicillin-susceptible isolates, susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin-resistant isolates, susceptibility is inferred from ampicillin.

[7] Susceptibility can be inferred from amoxicillin-clavulanic acid.

Susceptibility
The prevalence of acquired resistance can vary geographically and over time for selected species, and local data on resistance should be considered, especially in the treatment of severe infections. If local antimicrobial resistance prevalence raises concerns about the effectiveness of the drug in certain infections, expert consultation should be sought.

Classification of Relevant Species Based on Piperacillin/Tazobactam Susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive microorganisms *Enterococcus faecalis (*only isolates susceptible to ampicillin or penicillin*)* *Listeria monocytogenes* *Staphylococcus aureus* (only methicillin-susceptible isolates) *Staphylococcus* species, *coagulase-negative* (only methicillin-susceptible isolates)

Streptococcus agalactiae (Group B streptococci) † *Streptococcus pyogenes* (Group A streptococci) †
Aerobic Gram-negative microorganisms *Citrobacter koseri* *Haemophilus influenzae* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobic Gram-positive microorganisms *Clostridium* species *Eubacterium* species Anaerobic Gram-positive cocci††
Anaerobic Gram-negative microorganisms *Bacteroides fragilis* group *Fusobacterium* species *Porphyromonas* species *Prevotella* species
SPECIES WHERE ACQUIRED RESISTANCE MAY BE A CONCERN
Aerobic Gram-positive microorganisms *Enterococcus faecium* *Streptococcus pneumoniae*† *Streptococcus viridans group*†
Aerobic Gram-negative microorganisms *Acinetobacter baumannii* *Citrobacter freundii* *Enterobacter* species *Escherichia coli* *Klebsiella pneumoniae* *Morganella morganii* *Proteus vulgaris* *Providencia ssp.* *Pseudomonas aeruginosa* *Serratia* species
NATURALLY RESISTANT ORGANISMS
Aerobic Gram-positive microorganisms *Corynebacterium jeikeium*
Aerobic Gram-negative microorganisms *Burkholderia cepacia* *Legionella* species *Ochrobactrum anthropi* *Stenotrophomonas maltophilia*

Other microorganisms *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae*
†Streptococci are not β-lactamase-producing bacteria; resistance in these organisms arises from alterations in penicillin-binding proteins (PBPs). Therefore, susceptible isolates are only sensitive to piperacillin. Penicillin resistance in *S. pyogenes* has not been reported. †† Includes *Anaerococcus, Finegoldia, Parvimonas, Peptoniphilus, and Peptostreptococcus species*.

Merino Study (Bloodstream Infections Due to Extended-Spectrum Beta-Lactamase Producers)

In a prospective, non-inferiority, parallel-group, published randomized clinical trial comparing piperacillin/tazobactam to meropenem, the definitive (i.e., *in vitro*-confirmed susceptibility-based) treatment did not result in inferior 30-day mortality for adult patients with bloodstream infections caused by *E. coli* or *K. pneumoniae* resistant to ceftriaxone.

Among 191 patients randomized to receive meropenem, 7 (3.7%) met the primary 30-day mortality endpoint compared to 23 out of 187 patients (12.3%) randomized to piperacillin/tazobactam (risk difference, 8.6% [one-sided 97.5% CI −∞ to 14.5%]; P=0.90 for non-inferiority). The difference did not meet the 5% non-inferiority margin.

Effects, according to the protocol, the population analysis was consistent; 7 out of 186 patients (3.8%) in the meropenem group compared to 18 out of 170 patients (10.6%) in the piperacillin/tazobactam group met the primary outcome (risk difference, 6.8% [one-sided 97.5% CI, -∞ to 12.8]; P=0.76 for non-inferiority).

Clinical and microbiological improvement up to day 4 (secondary outcomes) occurred in 138 out of 185 patients (74.6%) randomized to meropenem, compared to 121 out of 177 patients (68.4%) in the piperacillin/tazobactam group (risk difference, 6.2% [95% CI, -15.5 to 3.1]; P=0.19). Statistical tests for secondary outcomes were two-tailed; a P-value of <0.05 was considered statistically significant.

In this study, a mortality imbalance was detected between the study groups. It was assumed that the deaths in the piperacillin/tazobactam group were associated with underlying diseases rather than concurrent infections.

5.2. Pharmacokinetic properties

General characteristics

Absorption:

The most common administration route is I.V. bolus injection. After a 4 g/0.5 g intravenous infusion administered over 30 minutes, the peak concentrations of piperacillin and tazobactam are 298 mcg/mL and 34 mcg/mL, respectively.

Distribution:
The plasma protein binding of piperacillin and tazobactam is approximately 30%. The binding of tazobactam and piperacillin is not affected by the presence of the other compound. The protein binding of tazobactam metabolites is negligible.

TIPRAXIN concentrations are widely distributed in tissues and body fluids, including the intestinal mucosa, gallbladder, bile, lungs, and bone. The average tissue concentration of TIPRAXIN is 50% to 100% of the plasma concentration. As with other penicillins, the distribution to cerebrospinal fluid is low in subjects with non-inflammatory meningitis.

Biotransformation:
Piperacillin is metabolized microbiologically to its minor desacetyl metabolite. Tazobactam is metabolized to a single metabolite, which is microbiologically inactive.

Elimination:
The renal elimination of piperacillin and tazobactam occurs via glomerular filtration and tubular secretion.

Piperacillin is primarily eliminated through the kidneys, with 68% of the dose excreted unchanged in the urine.
Tazobactam is primarily eliminated through the kidneys, with 80% of the dose excreted unchanged in the urine and the remaining dose excreted as metabolites. Piperacillin, tazobactam, and desacetyl piperacillin are also secreted into bile.

In healthy adults, following single or multiple doses, the plasma elimination half-life of the piperacillin and tazobactam combination ranges from 0.7 to 1.2 hours. These half-lives are not affected by the dosing or infusion duration. Both piperacillin and tazobactam's elimination half-lives increase with a decrease in renal clearance.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam. It is observed that tazobactam slightly reduces piperacillin clearance.

Linearity/Non-linearity:
TIPRAXIN exhibits linear pharmacokinetic properties.

Characteristics in Patients:

In renal dysfunction:
The half-life of TIPRAXIN increases with decreasing creatinine clearance. Compared to patients with normal kidney function, the increase in half-life for piperacillin and tazobactam is twofold and fourfold, respectively, in patients with creatinine clearance below 20 mL/min.

With 30 to 50% of piperacillin/tazobactam doses, tazobactam is eliminated from the body as a metabolite, with 5% of the tazobactam dose being removed by hemodialysis. 6% of the piperacillin dose and 21% of the tazobactam dose are transferred into the dialysis fluid via peritoneal dialysis, while up to 18% of the tazobactam dose is eliminated as a tazobactam metabolite.

In hepatic dysfunction:
The half-lives of piperacillin and tazobactam are prolonged in patients with liver dysfunction. However, dosage adjustments are not required in these patients.

In patients with hepatic cirrhosis, the half-lives of piperacillin and tazobactam are approximately 25% and 18% longer, respectively, compared to healthy volunteers.

Pediatric population:
In population pharmacokinetic analysis, the population mean (SE) value of 5.64 (0.34) mL/min/kg for 9- to 12-month-old patients' predicted clearance was comparable to that of adults.

In pediatric patients aged 2-9 months, the estimated piperacillin clearance is 80% of this value. The population mean (SE) volume of distribution for piperacillin is 0.243 (0.011) L/kg and is independent of age.

Geriatric population:
Compared to younger patients, elderly patients have an average half-life of piperacillin and tazobactam that is 32% and 55% longer, respectively. This difference may be due to age-related changes in creatinine clearance.

Race
In a study of healthy volunteers of Asian (n=9) and Caucasian (n=9) descent who received a single 4 g/0.5 g dose, no differences were observed in the pharmacokinetics of piperacillin and tazobactam.

5.3 Preclinical safety data

Non-clinical data do not present any specific risk to humans based on conventional studies on repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted for

piperacillin, tazobactam, or their combination.

A fertility and general reproduction study conducted in rats using intraperitoneal administration of tazobactam or piperacillin/tazobactam combination reported an increase in fetal abnormalities such as reduced abdominal size, delayed ossification, and rib variations, alongside maternal toxicity. Fertility of the F1 generation and embryonic development of the F2 generation were unaffected.

Teratogenic studies conducted on mice and rats with intravenous administration of tazobactam or piperacillin/tazobactam combination showed slight reductions in fetal weight in rats at maternally toxic doses, but no teratogenic effects were observed.
After intraperitoneal administration of tazobactam or piperacillin/tazobactam combination in rats, peri/postnatal development was impaired, coinciding with maternal toxicity (reduced pup weight, increased stillbirth, increased pup mortality).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains no excipients.

6.2 Incompatibilities

Due to unknown compatibility, piperacillin/tazobactam should not be mixed with other drugs in the syringe or infusion bottle. When taken with another antibiotic, TIPRAXIN should be administered separately. The in vitro mixing of TIPRAXIN with aminoglycosides may result in significant inactivation of the aminoglycoside.

Due to chemical instability, TIPRAXIN should not be used with solutions containing sodium bicarbonate alone.

TIPRAXIN IS INCOMPATIBLE WITH LACTATED RINGER'S SOLUTION.

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

6.3 Shelf life

24 months.

6.4 Special precautions for storage

The product should be stored as a dry powder at room temperature below 25ºC for up to 24 months.

After reconstitution with Water for Injection, 0.9% Isotonic Sodium Chloride Solution, or 5% Dextrose Solution, the solution is stable at room temperature below 25°C for 24 hours and at 2-

8°C for 48 hours.

For infusion: After dilution with Water for Injection, 0.9% Isotonic Sodium Chloride Solution, 5% Dextrose Solution, or 6% Dextran Solution, the diluted solution is stable at room temperature (below 25°C) for 24 hours and at 2-8°C for 48 hours.

6.5 Nature and contents of container

The product is provided in a transparent Type I glass vial with a bromobutyl rubber stopper and an aluminum flip-off cap. It is supplied in a cardboard box with one vial and a package insert.

6.6 Special precautions for disposal and other handling

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

Dilution Instructions:

Intravenous Injection: Each TIPRAXIN 2.25 g vial should be diluted with 10 mL of one of the following diluents.

Dilution Diluents: 0.9% Sodium Chloride Injection, Water for Injection, or 5% Dextrose. Each vial should be swirled until dissolved. Reconstitution should occur within 5-10 minutes with continuous mixing.

Intravenous Infusion: Each TIPRAXIN 2.25 g vial should be diluted with 10 mL of one of the diluents listed above. The diluted solution can then be further diluted to the desired volume (e.g., 50 mL to 150 mL) with one of the following intravenous diluents:

1. 0.9% Sodium Chloride Injection
2. Water for Injection **
3. 5% Dextrose
4. 6% Dextran (Isotonic Sodium Chloride)

** The recommended maximum volume of Water for Injection for each dose is 50 mL.

TIPRAXIN IS INCOMPATIBLE WITH LACTATED RINGER'S SOLUTION.

For intravenous infusion, one end of a sterile transfer needle should be attached to the vial containing the lyophilized powder, and the other end should be attached to a container with one of the above-mentioned diluents (50-150 mL). The solution should be swirled until it becomes clear. The infusion is then administered with the help of a bottle holder attached to the vial. The infusion should be administered over at least 30 minutes.

Use of TIPRAXIN with Aminoglycosides

Due to the *in vitro* inactivation of aminoglycosides by beta-lactam antibiotics, piperacillin/tazobactam and aminoglycosides should be administered separately. When combined treatment with aminoglycosides is recommended, piperacillin/tazobactam and aminoglycosides should be diluted and reconstituted separately.

7. MARKETING AUTHORIZATION HOLDER

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