SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TIPRAXIN 4 g/0.5 g Lyophilized Powder for Solution for IV Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each vial contains
Piperacillin sodium…….4.17 g (equivalent to 4 g piperacillin)
Tazobactam sodium……0.53 g (equivalent to 0.5 g tazobactam)

Excipient(s):
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder
Vials contain white to almost white sterile powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children over 12 years of age
TIPRAXIN is indicated for the treatment of:
- Complicated lower respiratory tract infections, including hospital-acquired pneumonia and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and deep tissue infections (including diabetic foot infections)

It is indicated for the treatment of patients with bacteremia associated or likely associated with the above infections.
TIPRAXIN may be used in the treatment of neutropenic patients with high fever due to suspected bacterial infection.

In children 2 to 12 years of age
- Complicated intra-abdominal infections

TIPRAXIN can be used in the treatment of neutropenic children with high fever due to 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 site of infection, its severity, and the type of pathogen.

The usual dosage for adults and children over 12 years of age is 4 g/0.5 g of TIPRAXIN every 8 hours.

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

This regimen can also be used to treat patients with other serious infections for which TIPRAXIN is indicated.

The following table shows the recommended dosage and frequency of treatment for adults and children over 12 years of age, based on symptoms:

Treatment frequency	**TIPRAXIN 4 g/0,5 g**
Once every 6 hours	Severe pneumonia
	Neutropenic adult patients with high fever suspected of having a bacterial infection
Once every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Complicated skin and deep tissue infections (including diabetic foot infections)

Pediatric patients aged 2-12 years
The table below shows the recommended dosage based on symptoms and body weight for pediatric patients aged 2-12 years:

Dosage based on weight and treatment frequency	Symptoms
80 mg piperacillin/10 mg tazobactam per kg every 6 hours	Neutropenic pediatric patients with high fever suspected of bacterial infection*
100 mg piperacillin/12.5 mg tazobactam per kg every 8 hours	Complicated intra-abdominal infections*

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

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

Method of administration:
TIPRAXIN should be given by slow intravenous injection (3-5 minutes) or by infusion (20-30 minutes).

See Section 6.6 for instructions on reconstitution of the drug before administration.

Additional information on special populations:
Renal impairment

In adults and children over 12 years of age with renal impairment, 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 is necessary.
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 will remove 30-50% of piperacillin within 4 hours, a supplemental dose of 2 g/250 mg TIPRAXIN should be administered after each dialysis period.

In pediatric patients aged 2 to 12 years with renal impairment, 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 adjustment required.
≤ 50	70 mg piperacillin/8.75 mg tazobactam/kg every 8 hours

In pediatric patients receiving hemodialysis, a booster dose of 40 mg piperacillin/5 mg/kg TIPRAXIN should be administered after each dialysis period.

Hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment.

Pediatric population:
The safety and efficacy of TIPRAXIN have not been established in patients younger than 2 years of age. No controlled clinical trial data are available.

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

4.3 Contraindications

TIPRAXIN is contraindicated in patients with

- Hypersensitivity to the active substance, any other penicillin-antibacterial agents or to any excipients.
- History of acute severe allergic reaction to beta-lactam active substances (including cephalosporins, monobactam, carbapenem).

4.4 Special warnings and precautions for use

When deciding on TIPRAXIN treatment, the appropriateness of using broad-spectrum semi-synthetic penicillin should be evaluated depending on factors such as the severity of the infection and the prevalence of resistance to other appropriate antibacterial agents.

Before initiating therapy with TIPRAXIN, 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 sometimes fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in some patients with a history of hypersensitivity to multiple allergens when treated with penicillins, including Piperacillin/tazobactam. If a serious hypersensitivity reaction occurs during treatment with TIPRAXIN, the antibiotic should be discontinued. Serious anaphylactic reactions may require adrenaline or other emergency treatment measures.

Serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrosis, 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 the patient develops a skin rash, he/she should be closely monitored and if the lesion progresses, TIPRAXIN should be discontinued.

Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In this case, TIPRAXIN should be discontinued.

Treatment with TIPRAXIN may result in the emergence of resistant organisms that may cause superinfection.

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 as a result of antibiotic therapy, the antibiotic should be discontinued and appropriate therapy instituted.

Leukopenia and neutropenia may occur, especially during long-term therapy. Therefore, periodic hematologic examinations 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).

Hypokalemia may occur in patients with low potassium reserves or in patients receiving concomitant medicinal products that may lower potassium levels; regular electrolyte determinations may be advisable in these patients.

Renal Impairment
Due to the potential for nephrotoxicity (see section 4.8), piperacillin/tazobactam should be used with caution in patients with renal impairment or on hemodialysis. The intravenous dose and frequency of administration should be adjusted according to the degree of renal impairment (see section 4.2).

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

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

This medicinal product contains 9.4 mmol (216 mg) of sodium per vial, equivalent to 10.8% of the WHO recommended adult maximum daily sodium intake of 2 g, due to the active ingredients piperacillin sodium and tazobactam sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Non-depolarizing muscle relaxants
Piperacillin is thought to play a role in prolonging the neuromuscular blockade of vecuronium when used concurrently with vecuronium. Based on similar mechanisms of action, the neuromuscular blockade produced by any non-depolarizing muscle relaxant can be expected to be prolonged in the presence of piperacillin.

Anticoagulants
Appropriate coagulation tests should be performed more frequently and monitored regularly during concomitant treatment with heparin, oral anticoagulants, and other medications that may affect the blood coagulation system, including platelet function.

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

Probenecid
As with other penicillins, concomitant use of probenecid and TIPRAXIN results in a longer half-life and lower renal clearance for piperacillin and tazobactam; however, peak plasma concentrations of either drug are not affected.

Aminoglycosides
Piperacillin, alone or in combination with tazobactam, does not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function or in patients with mild to moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and their M1 metabolites are also not significantly affected by tobramycin administration.

Inactivation of tobramycin and gentamicin by piperacillin has been observed in patients with severe renal impairment.

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

Vancomycin
Studies have found that combination therapy with piperacillin/tazobactam and vancomycin causes an increased incidence of acute kidney injury compared to vancomycin alone (see section 4.4). Some of these studies reported that the interaction was dose-dependent for vancomycin.

No pharmacokinetic interactions were found between piperacillin/tazobactam and vancomycin.

Drug-Laboratory Test Interactions:
As with other penicillins, non-enzymatic methods of measuring urine glucose may lead to false-positive results. Therefore, enzymatic urinary glucose measurement is necessary under TIPRAXIN treatment.

Chemical methods used to measure protein in urine 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 produce false-positive results in patients treated with piperacillin/tazobactam. Cross-reactivity with Non-*Aspergillus* polysaccharides and polyfuranoses has been reported with the Bio-Rad Laboratories *Platelia Aspergillus* EIA test.

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

Additional information regarding special populations
There are no interaction studies in special populations.

Pediatric population
There are no interaction studies in the pediatric population.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: B

Women of child-bearing potential/Birth control (Contraception)
Not sufficient information.

Pregnancy
There are no adequate studies on the use of TIPRAXIN during pregnancy.

Studies in animals have shown developmental toxicity at doses that were maternally toxic, but there was no evidence of teratogenicity (see section 5.3).

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

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/embryonic/fetal development/partum or postnatal development (see Section 5.3).

Caution should be exercised when administered to pregnant women.

Breastfeeding
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.

Reproductive ability / Fertility
A fertility study in rats showed no effects on fertility and mating after intraperitoneal administration of tazobactam or the piperacillin/tazobactam combination (see section 5.3).

4.7 Effects on ability to drive and use machines

No research has been conducted on the ability to drive and other types of machinery.

4.8 Undesirable effects

The most commonly reported side effect is diarrhea (observed in 1 out of 10 patients). In terms of the most serious side effects, pseudomembranous colitis and toxic epidermal necrolysis have been observed in 1 to 10 out of every 10,000 patients. The frequency of pancytopenia, anaphylactic shock, and Stevens-Johnson syndrome cannot be estimated based on the available data.

The adverse reactions listed below are classified by system organ class and using MedDRA preferred terms. Adverse reactions are listed in order of decreasing severity within each frequency group.

Undesirable effects are listed according to the following categories: 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); not known: cannot be estimated from the available data.

Infections and infestations
Common: Candida infection*
Rare: Pseudomembranous colitis

Blood and lymphatic system disorders
Common: Thrombocytopenia, anemia*
Uncommon: Leukopenia
Rare: Agranulocytosis
Not known: Pancytopenia*, neutropenia, hemolytic anemia*, thrombocytosis*, eosinophilia*

Immune system disorders
Not known: Anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*

Metabolism and nutritional disorders

Uncommon: Hypokalemia

Psychiatric disorders
Common: Insomnia
Not known: Delirium*

Nervous system disorders
Common: Headache,
Uncommon: Seizure*

Vascular disorders
Uncommon: Hypotension, thrombophlebitis, phlebitis, flushing

Respiratory, thoracic, and mediastinal disorders
Rare: Epistaxis
Not known: Eosinophilic pneumonia

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

Hepatobiliary disorders
Not known: Hepatitis*, jaundice

Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Erythema multiforme*, urticaria, maculopapular rash*
Rare: Toxic epidermal necrolysis*
Not known: 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

Renal and urinary disorders
Not known: Renal failure, tubulointerstitial nephritis*

General disorders and administration site conditions
Common: Fever, injection site reaction
Uncommon: Chills

Investigations
Common: Increased alanine aminotransferase, increased aspartate aminotransferase, decreased total blood protein, decreased blood albumin, positive Coombs direct test, increased blood creatinine, increased blood alkaline phosphatase, increased blood urea, and prolonged activated partial thromboplastin time
Uncommon: Decreased blood glucose, increased blood bilirubin, prolonged prothrombin time.

Not known: Prolonged bleeding time, increased gamma glutamyl transferase

*Adverse events identified after marketing

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

Effects of the beta-lactam antibiotic class
Beta-lactam antibiotics, including piperacillin and tazobactam, can cause signs 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
Overdose events associated with piperacillin/tazobactam have been reported since the product was marketed. The majority of these events, including nausea, vomiting, and diarrhea, have also been reported with the usual recommended doses. If higher than recommended doses are administered intravenously, patients may experience neuromuscular excitability or convulsions (especially in the presence of renal impairment).

Treatment
In the event of overdose, piperacillin/tazobactam therapy should be discontinued. There is no known specific antidote. Symptomatic and supportive treatment should be administered according to the patient's clinical condition.

Excessive serum piperacillin or tazobactam concentrations can be reduced by hemodialysis (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic Antibacterials, combinations of penicillins including 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 commonly cause resistance to penicillins and cephalosporins, but it does not inhibit AmpC enzymes or metallo beta-lactamases.
Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance only to piperacillin.

Pharmacokinetic/Pharmacodynamic Relationship
Time above minimum inhibitory concentration (T>MIC) is considered the major pharmacodynamic

determinant of efficacy for piperacillin.

Mechanism of resistance
The two main mechanisms of resistance to piperacillin/tazobactam are:
• Inactivation of piperacillin by the following beta-lactamases that are not inhibited by tazobactam: beta-lactamases of molecular classes B, C, and D. Additionally, tazobactam does not protect against extended-spectrum beta-lactamases of molecular classes A and D.
• Alterations in penicillin-binding proteins (PBPs) in bacteria, leading to a decrease in piperacillin affinity for the molecular target.

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

Breakpoints
EUCAST Clinical MIC Breakpoints for piperacillin/tazobactam (EUCAST Clinical Breakpoint Table Version 10.0, valid January 1, 2020). For susceptibility testing purposes, the tazobactam concentration is fixed at 4 mg/L.

Pathogen	**Species-related limit values (S≤/R>), mg/L piperacillin**
Enterobacterales (önceki adıyla *Enterobacteriaceae*)	8/16
Pseudomonas aeruginosa	<0,001/16[1]
Staphylococcus türleri	-[2]
Enterococcus türleri	-[3]
Streptococcus Grup A, B, C ve G	-[4]
Streptococcus pneumoniae	-[5]
Viridans group streptokoklar	-[6]
Haemophilus influenzae	0,25/0,25
Moraxella catarrhalis	-[7]
Gram-pozitive anaerobes (except *Clostridioides difficile*)	8/16
Gram-negative anaerobes	8/16
Non-species-related (PK/PD) breakpoints	4/16

[1]For several drugs, EUCAST has provided breakpoints that categorize wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the drug) as "Susceptible, high exposure (I)" rather than "Susceptible, standard dosage regimen (S)." Susceptible breakpoints for these organism-drug co-administration situations are listed as optional, "not to scale" breakpoints of S ≤ 0.001 mg/L.

[2]Most staphylococci are penicillinase producers, and some are resistant to methicillin. Both mechanisms render them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin, and ticarcillin. Staphylococci tested for susceptibility to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci resistant to benzylpenicillin but tested for susceptibility to cefoxitin are susceptible to concomitant β-lactamase inhibitors, the isoxazole penicillins (oxacillin, cloxacillin, and flucloxacillin), and nafcillin. For oral medications, care should be taken to ensure adequate exposure at the site of infection. Staphylococci tested for resistance to cefoxitin are resistant to all penicillins. Ampicillin-susceptible *S. saprophyticus* is mecA-negative and susceptible to ampicillin, amoxicillin, and piperacillin (with or without a beta-lactamase inhibitor).

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

[4]The susceptibility of *Streptococcus* groups A, B, C, and G to penicillins is determined by the susceptibility of *Streptococcus* group B to benzylpenicillin, excluding phenoxymethylpenicillin and isoxazole penicillins. *Streptococcus* groups A, B, C, and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor provides no clinical benefit.

[5]To exclude beta-lactam resistance mechanisms, an oxacillin 1 µg disk screening test or a benzylpenicillin MIC test will be used. All beta-lactam drugs for which clinical breakpoints are available, including those with "Note," can be reported as susceptible without further testing, except for cefaclor, which should be reported as "susceptible, high exposure" (I) if the screening is negative (oxacillin inhibition zone ≥20 mm or benzylpenicillin MIC ≤0.06 mg/L). *Streptococcus pneumoniae* does not produce beta-lactamase. Adding a beta-lactamase inhibitor provides no clinical benefit. Susceptibility is determined by ampicillin (MIC or zone diameter).

[6]For isolates susceptible to benzylpenicillin, susceptibility can be determined to either benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility can be determined to ampicillin.

[7]Sensitivity can be detected from amoxicillin-clavulanic acid.

Susceptibility
The prevalence of acquired resistance may vary geographically and over time for selected species, and local information on resistance is particularly desirable when treating severe infections. In cases where the prevalence of local drug resistance makes the effectiveness of a drug questionable in certain infections, specialist advice should be sought.

Grouping of related species according to piperacillin/tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive microorganisms *Enterococcus faecalis* (isolates susceptible only 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 IN WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
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 *Chlamydophila pneumoniae* *Mycoplasma pneumoniae*
† Streptococci are not β-lactamase-producing bacteria; resistance in these organisms results from changes in penicillin-binding proteins (PBPs), and therefore susceptible isolates are susceptible only to piperacillin. Penicillin resistance has not been reported in S. pyogenes. †† Including Anaerococcus, Finegoldia, Parvimonas, Peptoniphilus, and Peptostreptococcus spp.

Merino Study (Bloodstream infections due to extended-spectrum beta-lactamase producers)
In a prospective, non-inferiority, parallel-group, published randomized clinical trial, definitive (i.e., based on in vitro confirmed susceptibility) treatment with piperacillin/tazobactam compared with meropenem resulted in noninferior 30-day mortality in adult patients with ceftriaxone-nonsusceptible E. coli or K. pneumoniae bloodstream 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 patients (3.7%) randomized to meropenem (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% margin of non-inferiority.

Effects were consistent in the per-protocol population analysis, with 18 of 170 patients (10.6%) in the piperacillin/tazobactam group meeting the primary outcome compared with 7 of 186 patients (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 improvement by day 4 (secondary outcomes) occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 patients (74.6%) randomized to meropenem (risk difference, 6.2% [95% CI −15.5 to 3.1%]; P=0.19). Statistical tests for secondary outcomes were 2-sided, with P<0.05 considered significant.

In this study, a mortality imbalance was found between the study groups. Deaths in the piperacillin/tazobactam group were assumed to be related to underlying diseases rather than concurrent infection.

5.2 Pharmacokinetic properties

General properties
Absorption
The most common route of administration is IV bolus injection. Peak piperacillin and tazobactam

concentrations after 4 g/0.5 g administered by intravenous infusion over 30 minutes were 298 mcg/mL and 34 mcg/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.

TIPRAXIN concentrations are widely distributed in tissues and body fluids such as intestinal mucosa, gallbladder, lung, bile, and bone. The average tissue concentration of TIPRAXIN is between 50% and 100% in plasma. As with other penicillins, distribution into cerebrospinal fluid is low in subjects with non-purulent meningitis.

Biotransformation
Piperacillin is metabolized to the microbiologically active minor desethyl metabolite. Tazobactam is metabolized to a single metabolite that was found to be microbiologically inactive.

Elimination
Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.
Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine.
Tazobactam is excreted primarily by the kidneys, with 80% of the dose excreted unchanged in the urine and the remainder as metabolites. Piperacillin, tazobactam, and desethylpiperacillin are also excreted into the bile.

In healthy adults, the plasma elimination half-life of the combination of piperacillin and tazobactam ranges from 0.7 to 1.2 hours following single or multiple doses. These half-lives are not affected by the dose or infusion duration alone. The elimination half-lives of both piperacillin and tazobactam increase with decreasing renal clearance.

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

Linearity/Nonlinearity
TIPRAXIN shows linear pharmacokinetics.

Characteristics in special populations
Renal dysfunction
The half-life of TIPRAXIN 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.

Hemodialysis removes 30% to 50% of piperacillin/tazobactam, along with 5% of the tazobactam metabolite. Peritoneal dialysis removes 6% of piperacillin and 21% of tazobactam doses into the dialysate, while up to 18% of tazobactam doses are eliminated as tazobactam metabolites.

Hepatic dysfunction
The half-lives of piperacillin and tazobactam are increased in patients with hepatic impairment.

However, no dosage adjustment is necessary in patients with hepatic impairment.

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

Pediatric population
In a population pharmacokinetic analysis, estimated clearance for 9 month-old to 12 month-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 pediatric 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.

Geriatric population
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 for piperacillin, tazobactam or their combinations.

A fertility and general reproduction study conducted in rats using intraperitoneal administration of tazobactam or the piperacillin/tazobactam combination reported decreased abdomen size and an increase in fetuses with ossification delays and rib variations, concomitant with maternal toxicity. Fertility of the F1 generation and embryonic development of the F2 generation were not impaired.

Teratogenicity studies conducted with intravenous administration of tazobactam or the piperacillin/tazobactam combination to mice and rats resulted in slightly reduced rat fetal weights at maternally toxic doses but did not show teratogenic effects.

After intraperitoneal administration of tazobactam or the piperacillin/tazobactam combination to rats, peri/postnatal development was impaired (decreased pup weights, increased stillbirths, increased pup mortality) concomitant with maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains no excipients

6.2 Incompatibilities

TIPRAXIN should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established. Whenever TIPRAXIN is used concurrently with another antibiotic, the medicines must be administered separately. The *in vitro* mixing of TIPRAXIN with aminoglycosides can result in substantial inactivation of the aminoglycoside.

Due to chemical instability, TIPRAXIN should not be used in solutions containing only sodium bicarbonate.

TIPRAXIN IS INCOMPATIBLE WITH LACTATED RINGER'S SOLUTIONS.

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

6.3 Shelf life

Shelf life is 24 months.

6.4 Special precautions for storage

The storage condition of the product as dry powder is 24 months at room temperature below 25º C.

After reconstitution with water for injection, 0.9% Isotonic sodium chloride solution and 5% Dextrose solution, it is stable for 24 hours at room temperature below 25°C and 48 hours at 2-8°C.

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

6.5 Nature and contents of container

It is made of a clear Type I glass vial, a bromobutyl rubber stopper, and an aluminum flip-off cap. It is presented in a cardboard box with one vial and package leaflet.

6.6 Special precautions for disposal and other handling

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

Instructions for dilution:
Intravenous Injection: Each 4.5 g vial of TIPRAXIN should be reconstituted with 10 ml of one of the following diluents.
Diluents for reconstitution: 0.9% sodium chloride for injection, water for injection and 5% dextrose.

After dilution, each vial should be shaken by swirling until dissolved. With continuous mixing, reconstitution should occur within 5-10 minutes.

Intravenous Infusion: Each 4.5 g vial of TIPRAXIN should be reconstituted with 10 ml of one of the diluents. The reconstituted solution can then be diluted to the desired volume (e.g., 50 ml to 150 ml) with one of the following intravenous diluents:

1. 0.9% sodium chloride for injection
2. Water for injection**
3. 5% Dextrose
4. 6% Dextran (isotonic sodium chloride)

**Maximum recommended volume of water for injection per dose is 50 ml.

TIPRAXIN IS INCOMPATIBLE WITH LACTATED RINGER'S SOLUTIONS.

For intravenous infusion, place one end of a sterile transfer needle in the vial containing the lyophilized powder, and the other end in the package containing any of the diluents mentioned above (50-150 mL). Dilute and shake until clear. Administer as an infusion using the bottle hanger attached to the vial. Administer over at least 30 minutes.

Concomitant use of TIPRAXIN with aminoglycosides
Due to the in vitro inactivation of aminoglycosides by beta-lactam antibiotics, separate administration of piperacillin/tazobactam and aminoglycosides is recommended. When concomitant treatment with aminoglycosides is recommended, piperacillin/tazobactam and aminoglycosides should be diluted and reconstituted separately.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece - ISTANBUL/TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-mail:deva@devaholding.com.tr

8. MARKETING AUTHORIZATION NUMBER

2018/309

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 07.06.2018
Date of last renewal:

10. DATE OF REVISION OF THE TEXT