SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Trade name : Pbcet 1125™

Generic name : Ceftriaxone & Tazobactam for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A. Qualitative Composition

Each vial contains:

Ceftriaxone Sodium (sterile) USP

equivalent to Ceftriaxone 1000mg

Tazobactam Sodium (sterile) USP

Equivalent to Tazobactam 125 mg

For I.M./I.V. Use

B. Quantitative composition

Batch Size : 20000 Vials

S. No.	Materials	Specification	Label claim	Quantity/ Vials	Required quantity per batch
1.	Ceftriaxone Sodium	USP	1000 g.	1.195 g.	23.900 Kg
2.	Tazobactam Sodium	USP	125 mg	143.77 mg	2.875 kg
3.	Sterilised Water For Injections BP	BP	----	-----	20000 NO.

3. PHARMACEUTICAL FORM

Powder for reconstitution (intravenous /intramuscular)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PBCET CEFTRIAXONE. TAZOBACTAM is indicated for the treatment of the following infections in adult and paediatric patients (see sections 4.2 and 5.1):

Complicated intra-abdominal infections (see section 4.4);
Acute pyelonephritis;
Complicated urinary tract infections (see section 4.4).

PBCET CEFTRIAXONE. TAZOBACTAM is also indicated for the treatment of the following infection in adult patients (18 years or older) (see section 5.1):

Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

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

4.2 Posology and method of administration

Posology

The recommended intravenous dose regimen for adult patients with creatinine clearance > 50 mL/min is shown by infection type in Table 1.

Table 1: Intravenous dose of PBCET CEFTRIAXONE. TAZOBACTAM by type of infection in adult patients (18 years or older) with creatinine clearance* > 50 mL/min

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated intra-abdominal infection**	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	4-14 days
Complicated urinary tract infection Acute pyelonephritis	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	7 days
Hospital-acquired pneumonia, including ventilator-associated pneumonia***	2 g ceftolozane / 1 g tazobactam	Every 8 hours	1 hour	8-14 days

*Creatinine clearance estimated using Cockcroft-Gault formula.
**To be used in combination with metronidazole when anaerobic pathogens are suspected.
***To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

The recommended intravenous dose regimen for paediatric patients with estimated glomerular filtration rate (eGFR) > 50 mL/min/1.73 m^2 is shown by infection type in Table 2.

Table 2: Intravenous dose of PBCET CEFTRIAXONE. TAZOBACTAM by type of infection in paediatric patients (from birth* to below 18 years of age) with eGFR > 50 mL/min/1.73 m^2**

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated intra-abdominal infection***	20 mg/kg ceftolozane / 10 mg/kg tazobactam up to a maximum dose of 1 g ceftolozane / 0.5 g tazobactam****	Every 8 hours	1 hour	5-14 days*****
Complicated urinary tract infection Acute pyelonephritis	20 mg/kg ceftolozane / 10 mg/kg tazobactam up to a maximum dose of 1 g ceftolozane / 0.5 g tazobactam****	Every 8 hours	1 hour	7-14 days*****

*Defined as > 32 weeks gestational age and ≥ 7 days postnatal.
**eGFR estimated using Bedside Schwartz equation.
***To be used in combination with metronidazole when anaerobic pathogens are suspected.
****Children weighing > 50 kg should not exceed the maximum dose of 1 g ceftolozane / 0.5 g tazobactam.
*****The total treatment duration shown may include intravenous PBCET CEFTRIAXONE. TAZOBACTAM followed by appropriate oral therapy.

Special populations

Elderly (≥65 years of age)
No dose adjustment is necessary for the elderly based on age alone (see section 5.2).

Renal impairment
In patients with mild renal impairment (estimated creatinine clearance > 50 mL/min), no dose adjustment is necessary (see section 5.2).

In adult patients with moderate or severe renal impairment, and in adult patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table 3 (see sections 5.1 and 6.6).

Table 3: Recommended intravenous dose regimens for PBCET CEFTRIAXONE. TAZOBACTAM in adult patients (18 years or older) with creatinine clearance* ≤ 50 mL/min

Estimated creatinine clearance (mL/min)*	**Complicated intra-abdominal infections, complicated urinary tract infections, and acute pyelonephritis****	**Hospital-acquired pneumonia, including ventilator-associated pneumonia****
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours	1 g ceftolozane / 0.5 g tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
End stage renal disease on haemodialysis	A single loading dose of 500 mg ceftolozane / 250 mg tazobactam followed after 8 hours by a 100 mg ceftolozane / 50 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)	A single loading dose of 1.5 g ceftolozane / 0.75 g tazobactam followed after 8 hours by a 300 mg ceftolozane / 150 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)

*Creatinine clearance estimated using Cockcroft-Gault formula.
**All doses of PBCET CEFTRIAXONE. TAZOBACTAM are administered intravenously over 1 hour and are recommended for all indications. The duration of treatment should follow the recommendations in Table 1.

There is insufficient information to recommend a dose regimen for paediatric patients with moderate or severe renal impairment (eGFR ≤ 50 mL/min/1.73 m^2) or end stage renal disease (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Method of administration

PBCET CEFTRIAXONE. TAZOBACTAM is to be administered by intravenous infusion over a 1 hour period for all doses.

Precautions to be taken before handling or administering the product
See section 6.2 for incompatibilities.

See section 6.6 for instructions on reconstitution and dilution of the medicinal product before administration.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
Hypersensitivity to any cephalosporin antibacterial agent;
Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible (see sections 4.3 and 4.8). If a severe allergic reaction occurs during treatment with ceftolozane/tazobactam, the medicinal product should be discontinued and appropriate measures taken.

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterial agents may also be hypersensitive to ceftolozane/tazobactam.

Ceftolozane/tazobactam is contraindicated in patients with a history of hypersensitivity to ceftolozane, tazobactam, or cephalosporins (see section 4.3).

Ceftolozane/tazobactam is also contraindicated in patients with severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems) (see section 4.3).

Ceftolozane/tazobactam should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or other beta-lactam antibacterial agents.

Effect on renal function

A decline in renal function has been seen in adult patients receiving ceftolozane/tazobactam.

Impaired renal function

The ceftolozane/tazobactam dose should be adjusted based on renal function (see section 4.2, Table 3).

In clinical trials of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis, the efficacy of ceftolozane/tazobactam was lower in adult patients with moderate renal impairment compared with those with normal or mildly impaired renal function at baseline.

Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ceftolozane/tazobactam should be adjusted as necessary.

Limitations of the clinical data

Patients who were immunocompromised, patients with severe neutropenia, and patients with end stage renal disease on haemodialysis were excluded from clinical trials.

Complicated intra-abdominal infections
In a trial in adult patients with complicated intra-abdominal infections, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess (420/970 [43.3%] patients), of which 137/420 (32.6%) had diffuse peritonitis at baseline. Approximately 82% of all patients in the trial had APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of < 10 and 2.3% had bacteraemia at baseline. In the clinically evaluable (CE) patients, the clinical cure rates for ceftolozane/tazobactam were 95.9% in 293 patients aged less than 65 years and 87.8% in 82 patients aged 65 years or more.

Complicated urinary tract infections
Clinical efficacy data in adult patients with complicated lower urinary tract infection are limited. In a randomised active-controlled trial 18.2% (126/693) ofmicrobiologically evaluable (ME) patients had complicated lower urinary tract infection, including 60/126 patients who were treated with ceftolozane/tazobactam. One of these 60 patients had bacteraemia at baseline.

Clostridioides difficile-associated diarrhoea

Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftolozane/tazobactam (see section 4.8). These types of infection may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftolozane/tazobactam. In such circumstances, the discontinuation of therapy with ceftolozane/tazobactam and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Non-susceptible micro-organisms

The use of ceftolozane/tazobactam may promote the overgrowth of non-susceptible micro-organisms. If super infection occurs during or following treatment, appropriate measures should be taken.

Ceftolozane/tazobactam is not active against bacteria that produce beta-lactamase enzymes which are capable of both degrading ceftolozane and not inhibited by the tazobactam component (see section 5.1).

Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with ceftolozane/tazobactam (see section 4.8). In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment.

Sodium content

Ceftolozane/tazobactam contains 230 mg sodium per vial, equivalent to 11.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 265 mg sodium per vial, equivalent to 13.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No significant medicinal product interactions are anticipated between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) based on *in vitro* and *in vivo* studies.

In vitro studies demonstrated that ceftolozane, tazobactam and the M1 metabolite of tazobactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations.

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations.

Tazobactam is a substrate for OAT1 and OAT3. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. Co-administration of ceftolozane/tazobactam with OAT1 and OAT3 substrate furosemide in a clinical study did not significantly increase furosemide plasma exposures (geometric mean ratios of 0.83 and 0.87 for C_{max} and AUC, respectively). However, active substances that inhibit OAT1 or OAT3 (e.g., probenecid) may increase tazobactam plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ceftolozane/tazobactam in pregnant women. Tazobactam crosses the placenta. It is not known if ceftolozane crosses the placenta.

Animal studies with tazobactam have shown reproductive toxicity (see section 5.3) without evidence of teratogenic effects. Studies with ceftolozane in mice and rats have not shown evidence of reproductive toxicity or teratogenicity. Ceftolozane administered to rats during pregnancy and breast-feeding was associated with a decrease in auditory startle response in postnatal day (PND) 60 male pups (see section 5.3).

PBCET CEFTRIAXONE. TAZOBACTAM should only be used during pregnancy if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

It is unknown whether ceftolozane and tazobactam are excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from PBCET CEFTRIAXONE. TAZOBACTAM therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of ceftolozane and tazobactam on fertility in humans have not been studied. Fertility studies in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or intravenous administration of ceftolozane (see section 5.3).

4.7 Effects on ability to drive and use machines

PBCET CEFTRIAXONE. TAZOBACTAM may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of PBCET CEFTRIAXONE. TAZOBACTAM (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

PBCET CEFTRIAXONE. TAZOBACTAM was evaluated in Phase 3 comparator-controlled clinical trials of complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis) in adult patients.

The most common adverse reactions ($\geq$ 3% in pooled Phase 3 trials of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis) occurring in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM were nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

PBCET CEFTRIAXONE. TAZOBACTAM was evaluated in a Phase 3 comparator-controlled clinical trial ofadult patients with hospital- acquired pneumonia, including ventilator-associated pneumonia.

The most common adverse reactions ($\geq$ 5% in a Phase 3 trial of hospital-acquired pneumonia, including ventilator-associated pneumonia) occurring in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased and were generally mild or moderate in severity.

Tabulated list of adverse reactions

The following adverse reactions have been identified during adult clinical trials with PBCET CEFTRIAXONE. TAZOBACTAM . Adverse reactions are classified according to MedDRA system organ class and frequency. Frequency categories are derived according to the following conventions: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) (see Table 4).

Table 4: Adverse reactions identified during adult clinical trials with ceftolozane/tazobactam

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Infections and infestations	*Clostridioides difficile* colitis[2]	Candidiasis including oropharyngeal and vulvovaginal[1], *Clostridioides difficile* colitis[1], fungal urinary tract infection[1], *Clostridioides difficile* infection[2]
Blood and the lymphatic system disorders	Thrombocytosis[1]	Anaemia[1]
Metabolism and nutrition disorders	Hypokalemia[1]	Hyperglycaemia[1], hypomagnesaemia[1], hypophosphataemia[1]
Psychiatric disorders	Insomnia[1], anxiety[1]	
Nervous system disorders	Headache[1], dizziness[1]	Ischemic stroke[1]
Cardiac disorders		Atrial fibrillation[1], tachycardia[1], angina pectoris[1]
Vascular disorders	Hypotension[1]	Phlebitis[1], venous thrombosis[1]
Respiratory, thoracic, and mediastinal disorders		Dyspnoea[1]
Gastrointestinal disorders	Nausea[1], diarrhoea[3], constipation[1], vomiting[3], abdominal pain[1]	Gastritis[1], abdominal distension[1], dyspepsia[1], flatulence[1], ileus paralytic[1]
Skin and subcutaneous tissue disorders	Rash[1]	Urticaria[1]
Renal and urinary disorders		Renal impairment[1], renal failure[1]
General disorders and administration site conditions	Pyrexia[1], infusion site reactions[1]	
Investigations	Alanine aminotransferase increased[3], aspartate aminotransferase increased[3], transaminases increased[2], liver function test abnormal[2], blood alkaline phosphatase increased[2], gamma-glutamyltransferase increased[2]	Coombs test positive[3], increased serum gamma-glutamyl transpeptidase (GGT)[1], increased serum alkaline phosphatase[1], *Clostridioides* test positive[2]

[1] Specific for the complicated intra-abdominal infections, acute pyelonephritis, and complicated urinary tract infections indications treated with PBCET CEFTRIAXONE. TAZOBACTAM (1 g / 0.5 g intravenously every 8 hours) for up to 14 days.

[2] Specific for the hospital-acquired pneumonia, including ventilator-associated pneumonia indication treated with PBCET CEFTRIAXONE. TAZOBACTAM (2 g / 1 g intravenously every 8 hours) for up to 14 days.

[3] Applies across all indications: complicated intra-abdominal infections, acute pyelonephritis, complicated urinary tract infections, and hospital-acquired pneumonia, including ventilator-associated pneumonia.

Paediatric population

The safety assessment in paediatric patients, aged from birth to less than 18 years, is based on the safety data from two trials in which 70 patients with complicated intra-abdominal infections and 100 patients with complicated urinary tract infections (including acute pyelonephritis) received PBCET CEFTRIAXONE. TAZOBACTAM . The safety profile in these 170 paediatric patients was generally similar to that observed in the adult population with complicated intra-abdominal infections and complicated urinary tract
infections (including acute pyelonephritis). There were three additional adverse reactions observed in the paediatric population: neutropenia, increased appetite, and dysgeusia (all frequency common). The most common adverse reactions (≥ 2% in pooled paediatric phase 2 trials) occurring in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased. Safety data in patients less than 3 months ofage with complicated intra-abdominal infections are limited.

Description of selected adverse reactions

Laboratory values
The development of a positive direct Coombs test may occur during treatment with PBCET CEFTRIAXONE. TAZOBACTAM . The incidence of seroconversion to a positive direct Coombs test was 0.2% in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM and 0% in patients receiving the comparator in the adult complicated intra-abdominal infections and complicated urinary tract infections clinical trials. The incidence of seroconversion to a positive direct Coombs test was 31.2% in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM and 3.6% in patients receiving meropenem in the adult hospital-acquired pneumonia, including ventilator-associated pneumonia clinical trial. The incidence of seroconversion to a positive direct Coombs test was 45.3% in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM and 33.3% in patients receiving meropenem in the paediatric complicated intra-abdominal infection clinical trial. The incidence of seroconversion to a positive direct Coombs test was 29.7% in patients receiving PBCET CEFTRIAXONE. TAZOBACTAM and 8.7% in patients receiving meropenem in the paediatric complicated urinary tract infection clinical trial. In clinical studies, there was no evidence of haemolysis in patients who developed a positive direct Coombs test in any treatment group.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of PBCET CEFTRIAXONE. TAZOBACTAM . The highest single dose of PBCET CEFTRIAXONE. TAZOBACTAM used in clinical trials was 3 g / 1.5 g of ceftolozane/tazobactam administered to healthy volunteers.

In the event of overdose, PBCET CEFTRIAXONE. TAZOBACTAM should be discontinued and general supportive treatment given. PBCET CEFTRIAXONE. TAZOBACTAM can be removed by haemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the M1 metabolite of tazobactam were removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other cephalosporins and penems, ATC code: J01DI54.

Mechanism of action

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death.

Tazobactam is a beta-lactam structurally related to penicillins. It is an inhibitor of many molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes. See below.

Mechanisms of resistance

Mechanisms of bacterial resistance to ceftolozane/tazobactam include:

i. Production of beta-lactamases that can hydrolyse ceftolozane and which are not inhibited by tazobactam (see below)
ii. Modification of PBPs

Tazobactam does not inhibit all Class A enzymes.
In addition tazobactam does not inhibit the following types of beta-lactamase:

i. AmpC enzymes (produced by Enterobacterales)
ii. Serine-based carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemases [KPCs])
iii. Metallo-beta-lactamases (e.g., New Delhi metallo-beta-lactamase [NDM])
iv. Ambler Class D beta-lactamases (OXA-carbapenemases)

Pharmacokinetic/pharmacodynamic relationships

For ceftolozane the time that the plasma concentration exceeds the minimum inhibitory concentration of ceftolozane for the infecting organism has been shown to be the best predictor of efficacy in animal models of infection.

For tazobactam the PD index associated with efficacy was determined to be the percentage of the dose interval during which the plasma concentration of tazobactam exceeds a threshold value (%T > threshold). The time above a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in *in vitro* and *in vivo* non-clinical models.

Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

		Minimum Inhibitory Concentrations (mg/L)	
Pathogen	**Type of Infection**	**Susceptible**	**Resistant**
Enterobacterales	Complicated intra-abdominal infections* Complicated urinary tract infections* Acute pyelonephritis* Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 2	> 2
P. aeruginosa	Complicated intra-abdominal infections* Complicated urinary tract infections* Acute pyelonephritis* Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 4	> 4
H. influenzae	Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 0.5	> 0.5

*Based on 1 g ceftolozane / 0.5 g tazobactam intravenously every 8 hours.

**Based on 2 g ceftolozane / 1 g tazobactam intravenously every 8 hours.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to PBCET CEFTRIAXONE. TAZOBACTAM *in vitro*:

Complicated intra-abdominal infection/

Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Gram-positive bacteria
Streptococcus anginosus
Streptococcus constellatus
Streptococcus salivarius

Complicated urinary tract infection/, including pyelonephriti/

Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

Ho/pital-acquired pneumonia, including ventilator-a//ociated pneumonia

Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to PBCET CEFTRIAXONE. TAZOBACTAM in the absence of acquired mechanisms of resistance:
Citrobacter freundii
Citrobacter koseri
Klebsiella (Enterobacter) aerogenes
Morganella morganii
Proteus vulgaris
Serratia liquefaciens

In vitro data indicate that the following species are not susceptible to ceftolozane/tazobactam:
Staphylococcus aureus
Enterococcus faecalis
Enterococcus faecium

Paediatric population

PBCET CEFTRIAXONE. TAZOBACTAM was evaluated in two blinded, randomised, active-controlled clinical trials in paediatric patients from birth (defined as > 32 weeks gestational age and ≥ 7 days postnatal) to below 18 years of age, one in patients with complicated intra-abdominal infections (in combination with metronidazole),
and the other in patients with complicated urinary tract infections and acute pyelonephritis. The primary objectives in these studies were to assess safety and tolerability ofceftolozane/tazobactam; efficacy was a secondary descriptive endpoint. Patients below 18 years of age with eGFR < 50 mL/min/1.73 m^2 (estimated using Bedside Schwartz equation) were excluded from these clinical trials. Additionally, data in patients below 3 months ofage with complicated intra-abdominal infections are very limited (one patient in the PBCET CEFTRIAXONE. TAZOBACTAM arm). Clinical cure rate at TOC (MITT) was
80.0% (56/70) for PBCET CEFTRIAXONE. TAZOBACTAM compared to 100.0% (21/21) for meropenem in paediatric patients with complicated intra-abdominal infections. Microbiological eradication rate at TOC (mMITT) was 84.5% (60/71) for PBCET CEFTRIAXONE. TAZOBACTAM compared to 87.5% (21/24) for meropenem in paediatric patients with acute pyelonephritis and complicated urinary tract infections.

The European Medicines Agency has deferred the obligation to submit the results of studies with PBCET CEFTRIAXONE. TAZOBACTAM in one or more subsets of the paediatric population in hospital-acquired pneumonia, including ventilator-associated pneumonia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The C_{max} and AUC of ceftolozane/tazobactam increase approximately in proportion to dose within ceftolozane single-dose range of 250 mg to 3 g and tazobactam single-dose range of 500 mg to 1.5 g. No appreciable accumulation of ceftolozane/tazobactam is observed following multiple 1-hour IV infusions of 1 g / 0.5 g ceftolozane/tazobactam or 2 g / 1 g ceftolozane/tazobactam administered every 8 hours for up to 10 days in healthy adults with normal renal function. The elimination half-life ($t_{½}$) of ceftolozane or tazobactam is independent of dose.

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is low (approximately 16% to 21% and 30%, respectively). The mean (coefficient of variation CV%) steady-state volume of distribution of ceftolozane/tazobactam in healthy adult males (n=51) following a single 1 g / 0.5 g IV dose was 13.5 L (21%) and 18.2 L (25%) for ceftolozane and tazobactam, respectively, similar to extracellular fluid volume.

Following 1 hour intravenous infusions of 2 g / 1 g ceftolozane/tazobactam or adjusted based on renal function every 8 hours in ventilated adult patients with confirmed or suspected pneumonia (N=22), ceftolozane and tazobactam concentrations in pulmonary epithelial lining fluid were greater than 8 mcg/mL and 1 mcg/mL, respectively, over 100% of the dosing interval. Mean pulmonary epithelial-to-free plasma AUC ratios of ceftolozane and tazobactam were approximately 50% and 62%, respectively and are similar to those in healthy adult subjects (approximately 61% and 63%, respectively) receiving 1 g / 0.5 g ceftolozane/tazobactam.

Biotransformation

Ceftolozane is eliminated in the urine as unchanged parent substance and thus does not appear to be metabolised to any appreciable extent. The beta-lactam ring of tazobactam is hydrolysed to form the pharmacologically inactive, tazobactam metabolite M1.

Elimination

Ceftolozane, tazobactam and the tazobactam metabolite M1 are eliminated by the kidneys. Following

administration of a single 1 g / 0.5 g IV dose of ceftolozane/tazobactam to healthy male adults greater than 95% of ceftolozane was excreted in the urine as unchanged parent substance. More than 80% of tazobactam was excreted as the parent compound with the remaining amount excreted as the

tazobactam M1 metabolite. After a single dose of ceftolozane/tazobactam, renal clearance of ceftolozane (3.41 - 6.69 L/h) was similar to plasma clearance (4.10 - 6.73 L/h) and similar to the glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is eliminated by the kidney via glomerular filtration.

The mean terminal elimination half-life of ceftolozane and tazobactam in healthy adults with normal renal function is approximately 3 hours and 1 hour, respectively.

Linearity/non-linearity

The C_{max} and AUC of ceftolozane/tazobactam increase in proportion to dose. Plasma levels of ceftolozane/tazobactam do not increase appreciably following multiple IV infusions of up to 2.0 g / 1.0 g administered every 8 hours for up to 10 days in healthy adults with normal renal function. The elimination half-life ($t_{½}$) of ceftolozane is independent of dose.

Special populations

Renal impairment
Ceftolozane/tazobactam and the tazobactam metabolite M1 are eliminated by the kidneys.

The ceftolozane dose normalised geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in adults with mild, moderate, and severe renal impairment, respectively, compared to healthy adults with normal renal function. The respective tazobactam dose normalised geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. To maintain similar systemic exposures to those with normal renal function, dose adjustment is required (see section 4.2).

In adults with end stage renal disease on haemodialysis, approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by haemodialysis. The recommended dose in adults with end stage renal disease on haemodialysis with complicated intra-abdominal infections or complicated urinary tract infections (including acute pyelonephritis) is a single loading dose of 500 mg / 250 mg ceftolozane/tazobactam followed by a 100 mg / 50 mg maintenance dose of ceftolozane/tazobactam administered every 8 hours for the remainder of the treatment period. The recommended dose in adults with end stage renal disease on haemodialysis with hospital-acquired pneumonia, including ventilator-associated pneumonia is a single loading dose of 1.5 g / 0.75 g ceftolozane/tazobactam followed by a 300 mg / 150 mg maintenance dose of ceftolozane/tazobactam administered every 8 hours for the remainder of the treatment period. With haemodialysis, the dose should be administered immediately following completion of dialysis (see section 4.2).

Augmented renal clearance
Following a single 1-hour intravenous infusion of 2 g / 1 g ceftolozane/tazobactam to critically ill adults with CrCL greater than or equal to 180 mL/min (N=10), mean terminal half-life values of ceftolozane and tazobactam were 2.6 hours and 1.5 hours, respectively. Free plasma ceftolozane concentrations were greater than 8 mcg/mL over 70% of an 8-hour period; free tazobactam concentrations were greater than 1 mcg/mL over 60% of an 8-hour period. No dose adjustment of ceftolozane/tazobactam is recommended for hospital-acquired pneumonia, including ventilator-associated pneumonia in adults with augmented renal clearance.

Hepatic impairment
As ceftolozane/tazobactam does not undergo hepatic metabolism, the systemic clearance of ceftolozane/tazobactam is not expected to be affected by hepatic impairment. No dose adjustment is recommended for ceftolozane/tazobactam in subjects with hepatic impairment (see section 4.2).

Elderly
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in exposure were observed with regard to age. No dose adjustment of ceftolozane/tazobactam based on age alone is recommended.

Paediatric patients
For PBCET CEFTRIAXONE. TAZOBACTAM dose recommendations in paediatric patients with complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis, refer to Table 2 in section 4.2.

The pharmacokinetics of ceftolozane and tazobactam in paediatric patients (below 18 years of age) were evaluated in one Phase 1 study (in proven or suspected gram-negative infection) and two Phase 2 studies (in complicated intra-abdominal infections and in complicated urinary tract infections, including pyelonephritis). The data from these three studies were pooled and population pharmacokinetic modelling was conducted to estimate paediatric individual steady-state AUC and C_{max} as well as to perform simulations to assess PK/PD probability of target attainment (PTA).

The individual steady-state AUC and C_{max} for ceftolozane and tazobactam, in paediatric patients aged 2 to below 18 years with complicated intra-abdominal infections or complicated urinary tract infections were generally similar to adults. There is limited experience with the use of ceftolozane and tazobactam in paediatric patients below 2 years of age. The recommended dose regimens in these paediatric patients were based on simulations conducted using population pharmacokinetic models, and no clinically relevant differences in steady-state AUC and C_{max} are expected between paediatric patients under 2 years and older children and adults.

There was insufficient clinical pharmacokinetic data in paediatric patients with eGFR $\leq$ 50 mL/min/1.73 m^2 with complicated intra-abdominal infections or complicated urinary tract infections to recommend a dose regimen for paediatric patients with eGFR $\leq$ 50 mL/min/1.73 m^2.

Gender
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed for ceftolozane and tazobactam. No dose adjustment is recommended based on gender.

Ethnicity
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in ceftolozane/tazobactam AUC were observed in Caucasians compared to other ethnicities. No dose adjustment is recommended based on race.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity in adult and juvenile animals, or genotoxicity. Carcinogenicity studies with ceftolozane/tazobactam have not been conducted.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: ceftolozane administered to rats during pregnancy and breast-feeding was associated with a decrease in auditory startle response in postnatal day (PND) 60 male pups at maternal doses of 300 and 1 000 mg/kg/day. A dose of 300 mg/kg/day to rats was associated with a ceftolozane plasma exposure (AUC) value lower than the ceftolozane plasma AUC value at the highest recommended human dose of 2 grams every 8 hours.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam in the rat.

6. Pharmaceutical particulars

6.1 List of excipients

Sterilised Water for Injection 10 ml Ampoule

6.2 Incompatibilities

Vancomycin, amsacrine, aminoglycosides, and fluconazole are physically incompatible with ceftriaxone/tazobactam in admixtures. When any of these drugs are to be

administered concomitantly with ceftriaxone/tazobactam by intermittent I.V. infusion, it is recommended that they be given sequentially, with thorough flushing of the I.V. lines (with one of the compatible fluids) between the administrations.

Do not use diluents containing calcium, such as Ringer' s solution or Hartmann' s solution, to reconstitute ceftriaxone/tazobactam vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone calcium can also occur when ceftriaxone/tazobactam is mixed with calcium-containing solutions in the same I.V. administration line.

Ceftriaxone/tazobactam must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone/tazobactam and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between I.M. ceftriaxone and calcium-containing products (I.V. or oral).

Ceftriaxone/tazobactam should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility.

NOTE: Parenteral drug products should be inspected visually for particulate matter before administration.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store in a cool dry place, Protected from light.

6.5 Nature and contents of container

1.125g sterile powder for injection filled in 10 ml clear colourless glass vial duly labeled and sealed with flip-off seal, along with one ampoule of 10 ml WFI, packed in printed carton with insert.

7. Marketing authorization holder

PANGENE BIOTECH PVT LTD
ESUOLA AGO PALACE WAY OKOTA LAGOS

MANUFACTURER

EAST AFRICAN (INDIA) OVERSEAS, Plot No 1, Pharmacity Selaqui, Dehradun - 248011, Uttarakhand, India

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

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