ZERBAXA®▼ 1 g/0.5 g powder for concentrate for solution for infusion (ceftolozane and tazobactam sodium)

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics (SmPC) before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to MSD UK (tel: 01992 467272). By clicking the above link you will leave the MSD website and be taken to the MHRA website.

PRESENTATION: White to yellowish powder containing 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

USES: For the treatment of the following infections in adults: Complicated intra-abdominal infections; Acute pyelonephritis; Complicated urinary tract infections. Consider official guidance on the appropriate use of antibacterial agents.

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

Table 1: Intravenous dose of Zerbaxa by type of infection in patients 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

*To be used in combination with metronidazole when anaerobic pathogens are suspected.

Elderly (≥ 65 years of age): No dose adjustment necessary. *Renal impairment:* mild renal impairment (estimated creatinine clearance [CrCL] > 50 mL/min), no dose adjustment necessary; moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, adjust dose as listed in Table 2.

Table 2: Intravenous dose of ceftolozane/tazobactam in patients with creatinine clearance ≤ 50 mL/min

Estimated CrCL (mL/min)*	Recommended dose regimen for Zerbaxa (ceftolozane/tazobactam)**
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours
End stage renal disease on haemodialysis	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 remainder of treatment period (on haemodialysis days, administer dose at the earliest possible time following completion of haemodialysis)

*CrCL estimated using Cockcroft-Gault formula
**All doses of Zerbaxa are administered intravenously over 1 hour and are recommended for all indications.

Hepatic impairment: No dose adjustment necessary. *Paediatric population:* Safety and efficacy below 18 years of age not yet established. No data available.

For intravenous infusion. The infusion time is 1 hour for 1 g / 0.5 g of Zerbaxa. *See SmPC for precautions to be taken before handling or administering the product*

CONTRAINDICATIONS
Hypersensitivity to active substances or to any of the excipients; 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).

PRECAUTIONS

Hypersensitivity reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible. In case of severe allergic reaction during treatment, discontinue and take appropriate measures. Patients with history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterial agents may also be hypersensitive to ceftolozane/tazobactam. Use 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 patients receiving ceftolozane/tazobactam. *Impaired renal function:* Adjust ceftolozane/tazobactam dose based on renal function. In clinical trials the efficacy of ceftolozane/tazobactam was lower in patients with moderate renal impairment compared with those with normal or mildly impaired renal function at baseline. Monitor patients with renal impairment at baseline frequently for any changes in renal function during treatment and adjust dose as necessary.

Limitations of the clinical data: Immunocompromised and patients with severe neutropenia were excluded from clinical trials. In a trial in 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 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. Clinical efficacy data in patients with complicated lower urinary tract infection are limited.

Clostridium difficile-associated diarrhoea: Antibacterial-associated colitis and pseudomembranous colitis have been reported, ranging in severity from mild to life threatening. Consideration of this diagnosis is important in patients who present with diarrhoea during or after the administration of ceftolozane/tazobactam. In such cases, consider discontinuation of and use of supportive measures together with administration of specific treatment for *Clostridium difficile.* *Non-susceptible micro-organisms:* Overgrowth may be promoted by use of ceftolozane/tazobactam. In case of super infection during or following treatment, take appropriate measures. Ceftolozane/tazobactam is not active against bacteria that produce beta-lactamase enzymes which are not inhibited by tazobactam. *Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia:* Development of a positive direct antiglobulin test (DAGT) may occur during treatment. The incidence of DAGT seroconversion in patients receiving ceftolozane/tazobactam was 0.2% in the clinical trials. In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. *Sodium content:* For consideration while treating patients on controlled-sodium diet. Ceftolozane/tazobactam contains 10.0 mmol (230 mg) of sodium per vial. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 11.5 mmol (265 mg) of sodium.

Interaction with other medicinal products and other forms of interaction: No significant medicinal product interactions anticipated between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) based on *in vitro* and *in vivo* studies. 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.

Pregnancy: No data in humans. Tazobactam crosses the placenta. It is not known if ceftolozane crosses the placenta. Use only during pregnancy if expected benefit outweighs possible risks to the pregnant woman and foetus.

Breast-feeding: Unknown whether ceftolozane and tazobactam are excreted in human milk and risk to newborns/infants cannot be excluded. Either discontinue breast-feeding or discontinue/abstain from Zerbaxa therapy taking into account benefit of breast-feeding for the child and benefit of therapy for the woman. *Fertility:* Not studied in humans.

UNDESIRABLE EFFECTS: Refer to SmPC for complete information on side effects.
Zerbaxa was evaluated in Phase 3 comparator-controlled clinical trials of complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis), which included a total of 1,015 patients, treated with Zerbaxa (1 g / 0.5 g intravenously every 8 hours, adjusted to match renal function where appropriate) for up to 14 days. The most common adverse reactions (≥ 3% in pooled Phase 3 trials): nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

The following adverse reactions have been identified during clinical trials with Zerbaxa. Frequency categories are derived according to the following conventions: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).
Common: Thrombocytosis, hypokalemia, insomnia, anxiety, headache, dizziness, hypotension, nausea, diarrhoea, constipation, vomiting, abdominal pain, rash, pyrexia, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* Candidiasis including oropharyngeal and vulvovaginal, clostridium difficile colitis, fungal urinary tract infection, anaemia, hyperglycaemia, hypomagnesaemia, hypophosphataemia, ischaemic stroke, atrial fibrillation, tachycardia, angina pectoris, phlebitis, venous thrombosis, dyspnoea, gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic, urticaria, renal impairment, renal failure, Coombs test positive, increased gamma-glutamyl transpeptidase, increased serum alkaline phosphatase.

PACKAGE QUANTITIES AND BASIC NHS COST:
10 Vials: £670.30

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