**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Zerbaxa 1 g/0.5 g powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

After reconstitution with 10 mL diluent, the total volume of the solution in the vial is 11.4 mL, which contains 88 mg/mL of ceftolozane and 44 mg/mL of tazobactam.

Excipient with known effect

Each vial contains 10 mmol (230 mg) of sodium.

When the powder is reconstituted with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, the vial contains 11.5 mmol (265 mg) of sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to yellowish powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Zerbaxa 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).

Zerbaxa 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 Zerbaxa 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<br>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 Zerbaxa 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<br>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 Zerbaxa 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 Zerbaxa 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 Zerbaxa 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

Zerbaxa 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) of microbiologically 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).

Zerbaxa 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 Zerbaxa 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

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

## 4.8 Undesirable effects

Summary of the safety profile

Zerbaxa 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 (≥ 3% in pooled Phase 3 trials of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis) occurring in patients receiving Zerbaxa were nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

Zerbaxa was evaluated in a Phase 3 comparator-controlled clinical trial of adult patients with hospital-acquired pneumonia, including ventilator-associated pneumonia.

The most common adverse reactions (≥ 5% in a Phase 3 trial of hospital-acquired pneumonia, including ventilator-associated pneumonia) occurring in patients receiving Zerbaxa 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 Zerbaxa. 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 Zerbaxa (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 Zerbaxa (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 Zerbaxa. 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 Zerbaxa were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased. Safety data in patients less than 3 months of age 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 Zerbaxa. The incidence of seroconversion to a positive direct Coombs test was 0.2% in patients receiving Zerbaxa 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 Zerbaxa 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 Zerbaxa 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 Zerbaxa 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 Zerbaxa. The highest single dose of Zerbaxa used in clinical trials was 3 g / 1.5 g of ceftolozane/tazobactam administered to healthy volunteers.

In the event of overdose, Zerbaxa should be discontinued and general supportive treatment given. Zerbaxa 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*<br>Complicated urinary tract infections*<br>Acute pyelonephritis*<br>Hospital-acquired pneumonia, including ventilator-associated pneumonia** | ≤ 2 | > 2 |
| *P. aeruginosa* | Complicated intra-abdominal infections*<br>Complicated urinary tract infections*<br>Acute pyelonephritis*<br>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 Zerbaxa *in vitro*:

***Complicated intra-abdominal infections***

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 infections, including pyelonephritis***

Gram-negative bacteria
*Escherichia coli*
*Klebsiella pneumoniae*
*Proteus mirabilis*

***Hospital-acquired pneumonia, including ventilator-associated 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 Zerbaxa 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

Zerbaxa 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 of ceftolozane/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 of age with complicated intra-abdominal infections are very limited (one patient in the Zerbaxa arm). Clinical cure rate at TOC (MITT) was 80.0% (56/70) for Zerbaxa 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 Zerbaxa 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 Zerbaxa 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 Zerbaxa 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.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that one of the active ingredients, ceftolozane, may pose a risk to surface water organisms (see section 6.6).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Arginine
Citric acid, anhydrous

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

3 years.

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature or 4 days at 2 to 8 ºC. The medicinal product is photosensitive and should be protected from light when not stored in the original carton.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).

Store in the original package in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

20 mL vial (Type I clear glass) with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

### 6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

The powder for concentrate for solution for infusion for each vial is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following reconstitution the vial should be shaken gently to dissolve the powder. The final volume is

approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam) per vial.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

See section 4.2 for recommended dose regimens for Zerbaxa based on indication and renal function. The preparation for each dose is shown below.

Instructions for preparing adult doses in INFUSION BAG:

For preparation of the 2 g ceftolozane / 1 g tazobactam dose: Withdraw the entire contents from two reconstituted vials (approximately 11.4 mL per vial) using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1.5 g ceftolozane / 0.75 g tazobactam dose: Withdraw the entire contents from one reconstituted vial (approximately 11.4 mL per vial) and 5.7 mL from a second reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1 g ceftolozane / 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 300 mg ceftolozane / 150 mg tazobactam dose: Withdraw 3.5 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Instructions for preparing paediatric doses in INFUSION BAG or in INFUSION SYRINGE:

NOTE: The following procedure describes the steps to prepare 100 mL of stock solution with a final concentration of 10 mg/mL ceftolozane / 5 mg/mL tazobactam. The volume of this stock solution to be administered to the paediatric patient will be based on calculating the appropriate dose based on the patient's weight (see section 4.2). Detailed steps and calculations are provided.

1. Preparing the stock solution (100 mL of 10 mg/mL ceftolozane / 5 mg/mL tazobactam): Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 89 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.
2. Preparing the required volume of stock solution for infusion:
    a. Calculate the appropriate amount of Zerbaxa (in mg) to deliver the required dose to the paediatric patient. Based on this dose in mg, calculate the appropriate volume of

the 10 mg/mL ceftolozane / 5 mg/mL tazobactam stock solution to be administered. Refer to Table 5 below to confirm the calculations. Note that the table is NOT inclusive of all possible calculated doses but may be utilised to estimate the approximate volume to verify the calculation.

b. Transfer an appropriately calculated volume of stock solution to an adequately sized infusion bag or infusion syringe. Values shown in Table 5 are approximate, and it may be necessary to round to the nearest graduation mark of an appropriately sized syringe for smaller volumes.

**Table 5: Preparation of Zerbaxa for paediatric patients (from birth* to below 18 years of age) from the 100 mL stock solution of 10 mg/mL ceftolozane / 5 mg/mL tazobactam**

| Zerbaxa dose (mg/kg) | Weight (kg) | Calculated amount of ceftolozane (mg) | Calculated amount of tazobactam (mg) | Volume of stock solution to administer to patient (mL) |
|---|---|---|---|---|
| 20 mg/kg ceftolozane / 10 mg/kg tazobactam** | 50 and greater | 1 000 | 500 | 100 |
| | 40 | 800 | 400 | 80 |
| | 30 | 600 | 300 | 60 |
| | 20 | 400 | 200 | 40 |
| | 15 | 300 | 150 | 30 |
| | 10 | 200 | 100 | 20 |
| | 5 | 100 | 50 | 10 |
| | 3 | 60 | 30 | 6 |
| | 1.5 | 30 | 15 | 3 |

*Defined as > 32 weeks gestational age and ≥ 7 days postnatal.
**Children weighing > 50 kg and with eGFR > 50 mL/min/1.73 $m^2$ should not exceed the maximum dose of 1 g ceftolozane / 0.5 g tazobactam.

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment (see section 5.3). Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

## 7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1032/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2015
Date of latest renewal: 17 April 2020

## 10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

FAREVA Mirabel
Route de Marsat
Riom
63963, Clermont-Ferrand Cedex 9
France

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Zerbaxa 1 g / 0.5 g powder for concentrate for solution for infusion
ceftolozane / tazobactam

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

## 3. LIST OF EXCIPIENTS

Sodium chloride, arginine, citric acid, anhydrous

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
10 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original package in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1032/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Zerbaxa 1 g / 0.5 g powder for concentrate
ceftolozane / tazobactam

## 2. METHOD OF ADMINISTRATION

For IV use after reconstitution and dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Zerbaxa 1 g / 0.5 g powder for concentrate for solution for infusion**
ceftolozane / tazobactam

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Zerbaxa is and what it is used for

Zerbaxa is a medicine used to treat a range of bacterial infections. It contains two active substances:
- ceftolozane, an antibiotic that belongs to the group of "cephalosporins" and which can kill certain bacteria that can cause infection;
- tazobactam, which blocks the action of certain enzymes called beta-lactamases. These enzymes make bacteria resistant to ceftolozane by breaking down the antibiotic before it can act. By blocking their action, tazobactam makes ceftolozane more effective at killing bacteria.

Zerbaxa is used in all age groups to treat complicated infections within the abdomen, and kidney and urinary system.

Zerbaxa is also used in adults to treat an infection of the lungs called "pneumonia".

## 2. What you need to know before you take Zerbaxa

**Do not take Zerbaxa**
- if you are allergic to ceftolozane, tazobactam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to medicines known as "cephalosporins".
- if you have had a severe allergic reaction (e.g., severe skin peeling; swelling of the face, hands, feet, lips, tongue or throat; or difficulty swallowing or breathing) to certain other antibiotics (e.g., penicillins or carbapenems).

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Zerbaxa if you know you are, or have previously been allergic to cephalosporins, penicillins or other antibiotics.

Talk to your doctor or pharmacist if you develop diarrhoea while taking Zerbaxa.

Infections caused by bacteria that are not sensitive to Zerbaxa or caused by a fungus can occur during or following treatment with Zerbaxa. Tell your doctor if you think you may have another infection.

Treatment with Zerbaxa sometimes causes production of antibodies that react with your red blood cells. If you are told that you have an abnormal blood test (called Coombs test) tell your doctor that you are having or have recently had Zerbaxa.

**Children and adolescents**
This medicine should not be given to children under 18 years old to treat pneumonia because there is not enough information on use in this age group for the treatment of this infection.

**Other medicines and Zerbaxa**
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Some medicines may interact with ceftolozane and tazobactam. These include:
- Probenecid (a medicine for gout). This can increase the time it takes for tazobactam to leave your body.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will advise if you should receive Zerbaxa during pregnancy.

If you are breast-feeding, your doctor will advise you on whether you should stop breast-feeding or stop or avoid Zerbaxa therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for you.

**Driving and using machines**
Zerbaxa may cause dizziness, which can affect your ability to drive and use machines.

**Zerbaxa contains sodium**
This medicine contains 230 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 11.5% of the recommended maximum daily dietary intake of sodium for an adult. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 265 mg sodium in each vial. This is equivalent to 13.3% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to take Zerbaxa

Your doctor or other healthcare professional will give you this medicine into one of your veins through an infusion (a drip) lasting one hour. The dose of medicine given to you depends on whether or not you have kidney problems.

The dose depends on the type of infection that you have, where the infection is in your body and how serious the infection is. Your doctor will decide on the dose that you need.

**Use in adults**
The recommended dose of Zerbaxa is 1 g of ceftolozane and 0.5 g of tazobactam or 2 g of ceftolozane and 1 g of tazobactam every 8 hours, which is given into one of your veins (directly into the bloodstream).

Treatment with Zerbaxa normally lasts between 4 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

**Use in children and adolescents**
The recommended dose of Zerbaxa is 20 mg/kg of ceftolozane and 10 mg/kg of tazobactam every 8 hours, which is given into one of your veins (directly into the bloodstream). The dose should not exceed 1 g of ceftolozane and 0.5 g of tazobactam.

Treatment with Zerbaxa normally lasts between 5 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

**Patients with kidney problems**
Your doctor may need to reduce the dose of Zerbaxa or decide how often Zerbaxa is given to you. Your doctor may also want to test your blood to make sure you receive an appropriate dose, especially if you have to take this medicine for a long time.

**If you take more Zerbaxa than you should**
As this product is given by a doctor or other healthcare professional, it is very unlikely that you will be given too much Zerbaxa. However, if you have any concerns you should let your doctor, nurse or pharmacist know immediately.

**If you stop taking Zerbaxa**
If you think you have not been given a dose of Zerbaxa, tell your doctor or other healthcare professional immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor straight away if you get these symptoms as you may need urgent medical treatment:**
- Sudden swelling of your lips, face, throat or tongue; a severe rash; and, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening
- Diarrhoea that becomes severe or does not go away or stool that contains blood or mucus during or after treatment with Zerbaxa. In this situation, you should not take medicines that stop or slow bowel movement

<u>Adults treated for complicated infections within the abdomen, and kidney and urinary system</u>
**Common** side effects (may affect up to 1 in 10 people):
Headache, stomach ache, constipation, diarrhoea, nausea, vomiting, increase in liver enzymes (from blood tests), rash, fever (high temperature), decrease in blood pressure, decrease in potassium (from blood tests), increase in the number of certain types of blood cells known as platelets, dizziness, anxiety, difficulty sleeping, infusion site reactions

**Uncommon** side effects (may affect up to 1 in 100 people):
Inflammation of the large intestine due to *C. difficile* bacteria, inflammation of the stomach, abdominal distension, indigestion, excessive gas in stomach or bowel, obstruction of the intestine, yeast infection in the mouth (thrush), yeast infection of female genitalia, fungal urinary tract infection, increase in sugar (glucose) levels (from blood tests), decrease in magnesium levels (from blood tests), decrease in phosphate levels (from blood tests), ischemic stroke (stroke caused by reduced blood flow in brain), irritation or inflammation of a vein at injection site, venous thrombosis (blood clot in a vein), low red blood cell counts, atrial fibrillation (rapid or irregular heartbeat), fast heartbeat, angina pectoris (chest pain or feeling of tightness, pressure or heaviness in chest), itchy rash or swellings on the skin, hives, Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells), kidney problems, kidney disease, shortness of breath

Additional side effects observed in children and adolescents treated for complicated infections within the abdomen, and kidney and urinary system
**Common** side effects (may affect up to 1 in 10 people):
Increased appetite, low white blood cell counts, altered taste

Adults treated for an infection of the lungs called "pneumonia"
**Common** side effects (may affect up to 1 in 10 people):
Inflammation of the large intestine due to *C. difficile* bacteria, diarrhoea, vomiting, increase in liver enzymes (from blood tests)

**Uncommon** side effects (may affect up to 1 in 100 people):
Infection due to *C. difficile* bacteria, *C. difficile* test positive (from stool test), Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Zerbaxa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after "EXP." The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2 ºC – 8 ºC).

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Zerbaxa contains**
- The active substances are ceftolozane and tazobactam.
- Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam. For doses above 1 g ceftolozane and 0.5 g tazobactam, two vials are used.
- The other excipients are sodium chloride, arginine, and citric acid, anhydrous.

**What Zerbaxa looks like and contents of the pack**
Zerbaxa is a white to slightly yellow powder for concentrate for solution for infusion (powder for concentrate) supplied in a vial.

Zerbaxa is available in packs containing 20 mL Type I clear glass vial with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

**Marketing Authorisation Holder**
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

**Manufacturer**
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63963, Clermont-Ferrand Cedex 9
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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

Preparation of solutions

Each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

The powder for concentrate for solution for infusion for each vial is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following reconstitution the vial should be shaken gently to dissolve the powder. The final volume is approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam) per vial.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature or 4 days at 2 to 8 ºC. The medicinal product is photosensitive and should be protected from light when not stored in the original carton.

See section 4.2 of the Summary of Product Characteristics for recommended dose regimens for Zerbaxa based on indication and renal function. The preparation for each dose is shown below.

Instructions for preparing adult doses in INFUSION BAG:

For preparation of the 2 g ceftolozane / 1 g tazobactam dose: Withdraw the entire contents from two reconstituted vials (approximately 11.4 mL per vial) using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1.5 g ceftolozane / 0.75 g tazobactam dose: Withdraw the entire contents from one reconstituted vial (approximately 11.4 mL per vial) and 5.7 mL from a second reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1 g ceftolozane / 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 300 mg ceftolozane / 150 mg tazobactam dose: Withdraw 3.5 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Instructions for preparing paediatric doses in INFUSION BAG or in INFUSION SYRINGE:

NOTE: The following procedure describes the steps to prepare 100 mL of stock solution with a final concentration of 10 mg/mL ceftolozane / 5 mg/mL tazobactam. The volume of this stock solution to be administered to the paediatric patient will be based on calculating the appropriate dose based on the

patient's weight (see section 4.2 of the Summary of Product Characteristics). Detailed steps and calculations are provided.

1. Preparing the stock solution (100 mL of 10 mg/mL ceftolozane / 5 mg/mL tazobactam): Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 89 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.
2. Preparing the required volume of stock solution for infusion:
    a. Calculate the appropriate amount of Zerbaxa (in mg) to deliver the required dose to the paediatric patient. Based on this dose in mg, calculate the appropriate volume of the 10 mg/mL ceftolozane / 5 mg/mL tazobactam stock solution to be administered. Refer to Table 1 below to confirm the calculations. Note that the table is NOT inclusive of all possible calculated doses but may be utilised to estimate the approximate volume to verify the calculation.
    b. Transfer an appropriately calculated volume of stock solution to an adequately sized infusion bag or infusion syringe. Values shown in Table 1 are approximate, and it may be necessary to round to the nearest graduation mark of an appropriately sized syringe for smaller volumes.

**Table 1: Preparation of Zerbaxa for paediatric patients (from birth* to below 18 years of age) from the 100 mL stock solution of 10 mg/mL ceftolozane / 5 mg/mL tazobactam**

| Zerbaxa dose (mg/kg) | Weight (kg) | Calculated amount of ceftolozane (mg) | Calculated amount of tazobactam (mg) | Volume of stock solution to administer to patient (mL) |
|---|---|---|---|---|
| 20 mg/kg ceftolozane / 10 mg/kg tazobactam** | 50 and greater | 1 000 | 500 | 100 |
| | 40 | 800 | 400 | 80 |
| | 30 | 600 | 300 | 60 |
| | 20 | 400 | 200 | 40 |
| | 15 | 300 | 150 | 30 |
| | 10 | 200 | 100 | 20 |
| | 5 | 100 | 50 | 10 |
| | 3 | 60 | 30 | 6 |
| | 1.5 | 30 | 15 | 3 |

*Defined as > 32 weeks gestational age and ≥ 7 days postnatal.
**Children weighing > 50 kg and with eGFR > 50 mL/min/1.73 $m^2$ should not exceed the maximum dose of 1 g ceftolozane / 0.5 g tazobactam.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

**One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment. Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.**