ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 adults (see section 5.1):

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

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 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.

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 [CrCL] > 50 mL/min), no dose adjustment is necessary, see section 5.2).

In patients with moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table 2 (see sections 5.1 and 6.6).

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	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)

*CrCL 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.

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. No data are available.

Method of administration

Zerbaxa is for intravenous infusion.
The infusion time is 1 hour for 1 g / 0.5 g of Zerbaxa.

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 patients receiving ceftolozane/tazobactam.

Impaired renal function

The ceftolozane/tazobactam dose should be adjusted based on renal function (see section 4.2, Table 2).

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. 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 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 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.

Clinical efficacy data in 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 (cLUTI), including 60/126 patients who were treated with ceftolozane/tazobactam. One of these 60 patients had bacteraemia at baseline.

Clostridium 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 *Clostridium 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 not inhibited by tazobactam. 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. 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

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. This should be taken into consideration while treating patients on controlled-sodium diet.

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 lactation 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), 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) occurring in patients receiving Zerbaxa were nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

Tabulated list of adverse reactions

The following adverse reactions have been identified during 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 3).

Table 3: Adverse reactions identified during clinical trials with ceftolozane/tazobactam (N=1,015)

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

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 *Enterobacteriaceae*)
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 threshold concentration required is dependent on the organism and the amount and type of β-lactamase produced.

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	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1	> 1
P. aeruginosa	≤ 4	> 4

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

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
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris
Serratia liquefacians
Serratia marcescens

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

Paediatric population

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 complicated intra-abdominal infection and complicated urinary tract infection (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 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.

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.

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 hydrolyzed 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 normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects with normal renal function. The respective tazobactam dose normalized 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, dosage adjustment is required (see section 4.2).

In subjects with end stage renal disease on haemodialysis, approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by haemodialysis. The recommended dose in subjects with end stage renal disease on haemodialysis 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. With haemodialysis, the dose should be administered immediately following completion of dialysis (see section 4.2).

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 trend in exposure was observed with regard to age. No dose adjustment of ceftolozane/tazobactam based on age alone is recommended.

Paediatric patients

Safety and efficacy in paediatric patients have not been established.

Gender

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed for ceftolozane (116 males compared to 70 females) and tazobactam (80 males compared to 50 females). 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 (n = 156) compared to all other ethnicities combined (n = 30). 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 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 lactation 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 approximately equivalent to the ceftolozane plasma AUC value at the human therapeutic dose.

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

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

30 months.

After reconstitution, chemical and physical in-use stability has been demonstrated for 4 days at 2 to 8°C. 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, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT 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.

The preparations that follow relate to dose adjustments for renally impaired patients:

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 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.

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.

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

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

10. DATE OF REVISION OF THE TEXT

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 manufacturers responsible for batch release

MSD Italia S.r.l.
Via Fontana del Ceraso 7
03012 - Anagni (FR)
Italy

Laboratoires Merck Sharp & Dohme Chibret
Route de Marsat
Riom
63963, Clermont Ferrand Cedex 9
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the 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

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 adults to treat complicated infections within the abdomen, and kidney and urinary system infections.

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 because there is not enough information on use in this age group.

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 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. This should be taken into consideration if you are on a controlled-sodium diet.

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.

Adults
The recommended dose is one vial of Zerbaxa (containing 1 g of ceftolozane and 0.5 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.

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

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 heart beat, angina pectoris (chest pain or feeling of tightness, pressure or heaviness in chest), itchy rash or swellings on the skin, hives, Coombs test positive (from blood test), kidney problems, kidney disease, shortness of breath

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°C – 8°C).

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. 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.
- 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.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {month YYYY}.

Other sources of information

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

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

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT 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.

The preparations that follow relate to dose adjustments for renally impaired patients:

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 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.

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, chemical and physical in-use stability has been demonstrated for 4 days at 2 to 8°C. 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, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions and would normally not be longer than 24 hours at 2 to 8°C.

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