SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ZERBAXA® 1 g/0,5 g Lyophilised Powder for Solution for IV Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZERBAXA 1,5 g Lyophilised Powder for Solution for IV Infusion contains ceftolozane 1 g and tazobactam 0,5 g (equivalent to 0,537 g tazobactam sodium) when reconstituted.

3 PHARMACEUTICAL FORM

ZERBAXA 1,5 g (ceftolozane and tazobactam) for injection is a white to yellow sterile lyophilised powder for solution for IV infusion.

Reconstituted solution: ZERBAXA solution for infusion is clear and colourless to slightly yellow, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZERBAXA Lyophilised Powder for Solution for IV Infusion is indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:

Complicated Intra-abdominal Infections (cIAI)

ZERBAXA used in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections caused by the following Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus* and *Streptococcus salivarius.*

Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

ZERBAXA is indicated for the treatment of complicated urinary tract infections, including pyelonephritis, with or without concurrent bacteraemia, caused by the following Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa.*

Hospital Acquired Bacterial Pneumonia (HABP) and Ventilator Associated Bacterial Pneumonia (VABP)

ZERBAXA is indicated for the treatment of HABP and VABP, caused by the following Gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella (Enterobacter) aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* and *Serratia marcescens.*

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial medicines, ZERBAXA should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and

susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Paediatric Use

The safety and efficacy of ZERBAXA in children and adolescents below 18 years of age have not yet been established.

4.2 Posology and method of administration

Posology

The recommended dosage regimen of ZERBAXA for injection is 1,5 gram (g) (ceftolozane 1 g and tazobactam 0,5 g) for cIAI and cUTI and 3 g (ceftolozane 2 g and tazobactam 1 g) for hospital acquired bacterial pneumonia administered every 8-hours by intravenous infusion over 1-hour in patients 18 years or older and with creatinine clearance (CrCL) > 50 mL/min. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress as shown in **Table 1**.

Table 1: Dosage of ZERBAXA by Infection in Patients with Creatinine Clearance (CrCl) > 50 mL/min

Infection	Dose	Frequency	Infusion Time (hours)	Duration of Treatment

Complicated Intra-abdominal Infections*	1,5 g ZERBAXA (1 g ceftolozane/0,5 g tazobactam)	Every 8-hours	1	4 to 14 days
Complicated Urinary Tract Infections, including Pyelonephritis	1,5 g ZERBAXA (1 g ceftolozane/0,5 g tazobactam)	Every 8-hours	1	7 days
Hospital Acquired Bacterial Pneumonia and Ventilator Associated Bacterial Pneumonia	3 g ZERBAXA (2 g ceftolozane/1 g tazobactam)	Every 8-hours	1	8 to 14 days

*Used in conjunction with metronidazole 500 mg intravenously every 8-hours.

Special populations

Renal Impairment

Dose adjustment is required for patients whose CrCL is 50 mL/min or less. Renal dose adjustments are listed in **Table 2**. For patients with changing renal function, monitor CrCL at least daily and adjust the dosage of ZERBAXA accordingly (see section 4.4).

Table 2: Recommended Dosage Regimens for ZERBAXA in Patients with Renal Impairment

Estimated CrCL (mL/min)*	**Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections† including Pyelonephritis**	**Hospital Acquired Bacterial Pneumonia (HABP) and Ventilator Associated Bacterial Pneumonia (VABP)†**
30 to 50	750 mg (500 mg and 250 mg) intravenously every 8-hours	1,5 g (1 g and 0,5 g) intravenously every 8-hours
15 to 29	375 mg (250 mg and 125 mg) intravenously every 8-hours	750 mg (500 mg and 250 mg) intravenously every 8-hours
End stage renal disease (ESRD) on haemodialysis (HD)	A single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 mg and 50 mg) maintenance dose administered every 8-hours for the remainder of the treatment period. With	A single loading dose of 2,25 g (1,5 g and 0,75 g) followed by a 450 mg (300 mg and 150 mg) maintenance dose administered every 8-hours for the remainder of the

	haemodialysis, the dose should be administered immediately following completion of dialysis.	treatment period (on haemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

*CrCL estimated using Cockcroft-Gault formula.

†All doses of ZERBAXA are administered over 1-hour.

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

Elderly (≥ 65 years of age)

No dose adjustment is necessary for the elderly based on age alone.

ZERBAXA is substantially excreted by the kidney and the risk of adverse reactions to

ZERBAXA may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Adjust dosage for elderly patients based on renal function.

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

Preparation of solutions

ZERBAXA does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

Constitute each vial of ZERBAXA with 10 mL of Sterile Water for injection or 0,9 % Sodium Chloride for injection, USP and gently shake to dissolve. The final volume is approximately 11,4 mL per vial.

CAUTION: THE CONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

To prepare the required dose, withdraw the appropriate volume determined from **Table 3** from the reconstituted vial(s). Add the withdrawn volume to an infusion bag containing 100 mL of 0,9 % Sodium Chloride for Injection, USP or 5 % Dextrose Injection, USP.

Table 3: Preparation of doses

ZERBAXA (ceftolozane and tazobactam) Dose	Volume to Withdraw from Reconstituted Vial(s)

3 g (2 g and 1 g)	Two vials of 11,4 mL each (entire contents from two vials)
2,25 g (1,5 g and 0,75 g)	11,4 mL from one vial (entire contents) and 5,7 mL from a second vial
1,5 g (1 g and 0,5 g)	11,4 mL (entire contents from one vial)
750 mg (500 mg and 250 mg)	5,7 mL
450 mg (300 mg and 150 mg)	3,5 mL
375 mg (250 mg and 125 mg)	2,9 mL
150 mg (100 mg and 50 mg)	1,2 mL

Inspect medicine products visually for particulate matter and discoloration prior to use. ZERBAXA infusions range from clear, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

Storage of constituted solutions

Upon constitution with Sterile Water for Injection or 0,9 % Sodium Chloride injection, reconstituted ZERBAXA solution may be held for 1-hour prior to transfer and dilution in a suitable infusion bag.

Following dilution of the solution with 0,9 % Sodium Chloride or 5 % Dextrose, ZERBAXA is stable for 24-hours when stored at room temperature or 7 days when stored under refrigeration at 2 to 8 °C.

Constituted ZERBAXA solution or diluted ZERBAXA infusion should not be frozen. Although physical and chemical stability has been proven for 48-hours at 2 to 8 °C and 24-hours at 25 °C from a microbiological point of view the solution should be used immediately after preparation.

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 °C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

4.3 Contraindications

ZERBAXA is contraindicated in patients with:

- Hypersensitivity to ceftolozane, tazobactam or to any of the inactive excipients.
- Hypersensitivity to any cephalosporin antibacterial medicines.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial medicines (e.g. penicillins or carbapenems).

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Impaired renal function

The ZERBAXA dose should be adjusted based on renal function (see section 4.2).

In a subgroup analysis of a Phase 3 intra-abdominal infection trial, clinical cure rates were lower in patients with baseline CrCL of 30 to ≤ 50 mL/min compared to those with CrCL > 50 mL/min. The reduction in clinical cure rates was more marked in the ZERBAXA plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the urinary tract infection trial. Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ZERBAXA should be adjusted as necessary.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial medicines. Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins or other beta-lactams. If ZERBAXA is to be given to a patient with a cephalosporin, penicillin or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA occurs, discontinue ZERBAXA and institute appropriate therapy.

***Clostridium difficile*-associated diarrhoea**

Clostridium difficile-associated diarrhoea (CDAD) has been reported for nearly all systemic antibacterial medicines, including ZERBAXA, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines alters the normal flora of the colon and may permit overgrowth of *C. difficile* (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 ZERBAXA. In such circumstances, the discontinuation of therapy with ZERBAXA and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered.

Development of drug resistant bacteria

Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

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.

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.

Limitations of the clinical data

Patients who were immunocompromised and patients with severe neutropenia were excluded from clinical trials.

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 (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

No significant interactions are anticipated between ZERBAXA and medicines that are substrates, inhibitors and inducers of cytochrome P450 enzymes.

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. A clinical interaction study was conducted, and results indicated interactions involving CYP1A2 and CYP3A4 inhibition by ZERBAXA are not anticipated.

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 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 µg/mL, respectively. Co-administration of ceftolozane and 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. Co-administration of tazobactam with the OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71 %.

Additional information on special populations

Renal impairment

Dosage adjustment is required in patients with moderate (CrCL 30 to 50 mL/min) or severe (CrCL 15 to 29 mL/min) renal impairment and in patients with end-stage renal disease on haemodialysis (see sections 4.2 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been established.

Breastfeeding

Women receiving ZERBAXA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

ZERBAXA may have an influence on the ability to drive and use machines. Dizziness may occur following administration of ZERBAXA.

4.8 Undesirable effects

Clinical Trials Experience

Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, including Pyelonephritis

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 (1,5 g every 8-hours, adjusted based on renal function where appropriate)] for up to 14 days.

a. Summary of the safety profile

The most common side effects (≥ 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.

ZERBAXA was evaluated in a Phase 3 comparator-controlled clinical trial of hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia.

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

b. Tabulated summary of adverse reactions

Side effects have been identified during clinical trials with ZERBAXA. Side effects 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 5**).

Table 5: 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	*Clostridioides difficile* colitis[2]	candidiasis including oropharyngeal and vulvovaginal[1], *Clostridium difficile* colitis[1], fungal urinary tract infection, *Clostridioides difficile* infection[2]
Blood and the lymphatic system disorders	thrombocytosis[1]	anaemia[1]
Metabolism and nutrition disorders	hypokalaemia[1]	hyperglycaemia[1], hypomagnesaemia[1], hypophosphatemia[1]
Psychiatric disorders	insomnia[1], anxiety[1]	
Nervous system disorders	headache[1], dizziness[1]	ischaemic 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 bacterial pneumonia, including ventilator-associated bacterial 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 bacterial pneumonia, including ventilator-associated bacterial pneumonia.

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 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 hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked

to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In the event of overdose, discontinue ZERBAXA and provide general supportive treatment. ZERBAXA can be removed by haemodialysis. Approximately 66 % of ceftolozane, 56 % of tazobactam and 51 % of the tazobactam metabolite M1 were removed by dialysis. No information is available on the use of haemodialysis to treat overdosage.

5 PHARMACOLOGICAL PROPERTIES

A.20.1.1 Broad and medium spectrum antibiotics

5.1 Pharmacodynamic properties

ZERBAXA (ceftolozane and tazobactam) is an antibacterial combination product consisting of the cephalosporin antibacterial, ceftolozane sulphate and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.

Ceftolozane sulphate is a semi-synthetic antibacterial of the beta-lactam class for parenteral administration.

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. Ceftolozane is an inhibitor to PBPs of *P. aeruginosa* (e.g. PBP1b, PBP1c and PBP3) *and E.coli* (e.g. PBP3).

Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Tazobactam is beta-lactam structurally related to penicillin. It is an inhibitor of many molecular Class A beta-lactamases, including CTX M, SHV and TEM enzymes (see **Resistance**).

Resistance

In vitro data indicate that the following species are not susceptible to ceftolozane/tazobactam:

- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium.*

Mechanisms of bacterial resistance to ceftolozane and tazobactam include:

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

Tazobactam does not inhibit all Class A enzymes.

In addition, tazobactam does not inhibit the following types of beta-lactamase:

- Serine-based carbapenemases (e.g. *Klebsiella pneumoniae* carbapenemases [KPCs])
- Metallo-beta-lactamases (e.g. New Delhi metallo-beta-lactamase [NDM])

- Ambler Class D beta-lactamases (OXA-carbapenemases).

Culture and susceptibility information and local epidemiology should be considered in selecting or modifying antibacterial therapy.

Cross-Resistance

Isolates resistant to other cephalosporins may be susceptible to ceftolozane and tazobactam, although cross resistance may occur.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of ZERBAXA (ceftolozane and tazobactam) in healthy adults with normal renal function after multiple 1-hour intravenous infusions of ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) administered every 8-hours are summarised in **Table 6**. Pharmacokinetic parameters are similar following single- and multiple-dose administration. The C_{max} and AUC of ceftolozane and tazobactam increase in proportion to dose. The elimination half-life ($t_{1/2}$) of ceftolozane or tazobactam is independent of dose.

Table 6: Mean (CV %) Steady-State Plasma Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) after Multiple Intravenous 1-hour Infusions of ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) every 8-hours in Healthy Adults

PK Parameters	ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g)		ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g)	
	Ceftolozane (n=10)	Tazobactam (n=10)	Ceftolozane (n=7)	Tazobactam (n=7)
C_{max} (µg/mL)	74,4 (14)	18,0 (8)	112 (13)	25,8 (15)
t_{max} (h)†	1,07 (1,00, 1,10)	1,01 (1,00, 1,10)	1,0 (1,0, 1,0)	1,0 (0,5, 1,0)
$AUC_{0-8,ss}$ (µg•h/mL)‡	182 (15)	25,0 (15)	300 (9,8)	40,5 (13)
$t_{½}$ (h)	3,12 (22)	1,03 (19)	2,8 (14)	1,0 (18)

†Median (minimum, maximum)

Steady-state AUC for 8-hour dosing interval. Daily AUC at steady-state is calculated by multiplying the AUC values by 3 (e.g. 546 µg•h/mL for ceftolozane and 75 µg•h/mL for tazobactam at the ceftolozane 1 g and tazobactam 0,5 g dosing regimen)

.

The mean steady-state population pharmacokinetic parameters of ZERBAXA in patients with cIAI and cUTI receiving 1-hour intravenous infusion of ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) or patients with hospital acquired bacterial pneumonia receiving 1-hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) every 8-hours are summarised in **Table 7**.

Table 7: Mean (CV%) Steady-State Plasma Population Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) after Multiple Intravenous 1-hour Infusions of

ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) every 8-hours in Patients with CrCL > 50 mL/min

PK Parameters	ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) in cIAI and cUTI Patients		ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) in Hospital Acquired Bacterial Pneumonia Patients	
	Ceftolozane (n=317)	**Tazobactam (n=244)**	**Ceftolozane (n=247)**	**Tazobactam (n=247)**
C_{max} (µg/mL)	65,7 (41)	17,8 (51)	105 (44)	26,4 (49)
$AUC_{0-8,ss}$ (µg•h/mL)	186 (40)	35,8 (160)	392 (60)	73,3 (104)
$t_{½}$ (h)	2,7 (32)	1,8 (83)	3,9 (50)	3,2 (61)

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is approximately 16 % to 21 % and 30 %, respectively. The mean (CV %) steady-state volume of distribution of ZERBAXA in healthy adult males (n=51) following a single intravenous dose of ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) 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 ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) or adjusted based on renal function every 8-hours in ventilated patients with confirmed or

suspected bacterial pneumonia (N=22), ceftolozane and tazobactam concentrations in pulmonary epithelial lining fluid were > 8 µg/mL and 1 µg/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 subjects (approximately 61 % and 63 %, respectively) receiving ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g).

Metabolism

Ceftolozane is mainly eliminated in the urine as unchanged parent drug 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 ZERBAXA 1,5 g (ceftolozane 1 g and tazobactam 0,5 g) intravenous dose 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 remainder excreted as the tazobactam M1 metabolite. After a single dose of ZERBAXA, renal clearance of ceftolozane (3,41 to 6,69 L/h) was similar to plasma clearance (4,10 to 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.

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 subjects with mild, moderate and severe renal impairment, respectively, compared to healthy subjects 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, dosage adjustment is required (see section 4.2).

In subjects with ESRD (end-stage renal disease) on HD (haemodialysis), approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by HD. The recommended dose in complicated intra-abdominal infections, complicated urinary tract infections and acute pyelonephritis subjects with ESRD on HD is a single loading dose of ZERBAXA 750 mg (ceftolozane 500 mg and tazobactam 250 mg), followed by a maintenance dose of ZERBAXA 150 mg (ceftolozane 100 mg and tazobactam 50 mg) administered every 8-hours for the remainder of the treatment period (see section 4.2). The recommended dose in hospital acquired bacterial pneumonia subjects with ESRD on HD is a single loading dose of ZERBAXA 2,25 g (ceftolozane 1,5 g and tazobactam 0,75 g), followed by a ZERBAXA 450 mg (ceftolozane

300 mg and tazobactam 150 mg) maintenance dose administered every 8-hours for the remainder of the treatment period. With HD, 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 ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) to critically ill patients with CrCL ≥ 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 > 8 µg/mL over 70 % of an 8-hour period; free tazobactam concentrations were > 1 µg/mL over 60 % of an 8-hour period. No dose adjustment of ZERBAXA is recommended for hospital acquired bacterial pneumonia patients 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 ZERBAXA in subjects with hepatic impairment (see section 4.2).

Elderly

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

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride as a stabilising agent, citric acid as a chelating agent and L-arginine.

Sugar free.

Excipients with known effect

Sodium content. 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.

6.2 Incompatibilities

Compatibility of ZERBAXA with other drugs has not been established. ZERBAXA should not be mixed with other drugs or physically added to solutions containing other drugs.

6.3 Shelf life

36 months when stored in 20 mL Type I clear glass vials with bromobutyl rubber stoppers packed and stored at 2 to 8 °C, protected from light.

6.4 Special precautions for storage

ZERBAXA vials should be stored in a refrigerator (2 to 8 °C) and protected from light.

Constituted ZERBAXA solution or diluted ZERBAXA infusion should not be frozen. Although physical and chemical stability has been proven for 48-hours at 2 to 8 °C and 24-hours at 25 °C from a microbiological point of view the solution should be used immediately after preparation.

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 °C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

After reconstitution, chemical and physical in-use stability has been demonstrated for 7 days when stored in a refrigerator (2 to 8 °C).

For single use only. Discard any unused portion.

Keep out of reach of children.

6.5 Nature and contents of container

ZERBAXA is available as a 20 mL Type I clear glass vial with a grey siliconized stopper (bromobutyl rubber) and sealed with purple, aluminium and plastic flip-off seal.

Outer carton: The 20 mL vial is packed in a cardboard carton with the package insert and patient information leaflet.

Pack size of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8 REGISTRATION NUMBER

51/20.1.1/0840

9 DATE OF FIRST AUTHORISATION

27 October 2020

10 DATE OF REVISION OF THE TEXT

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